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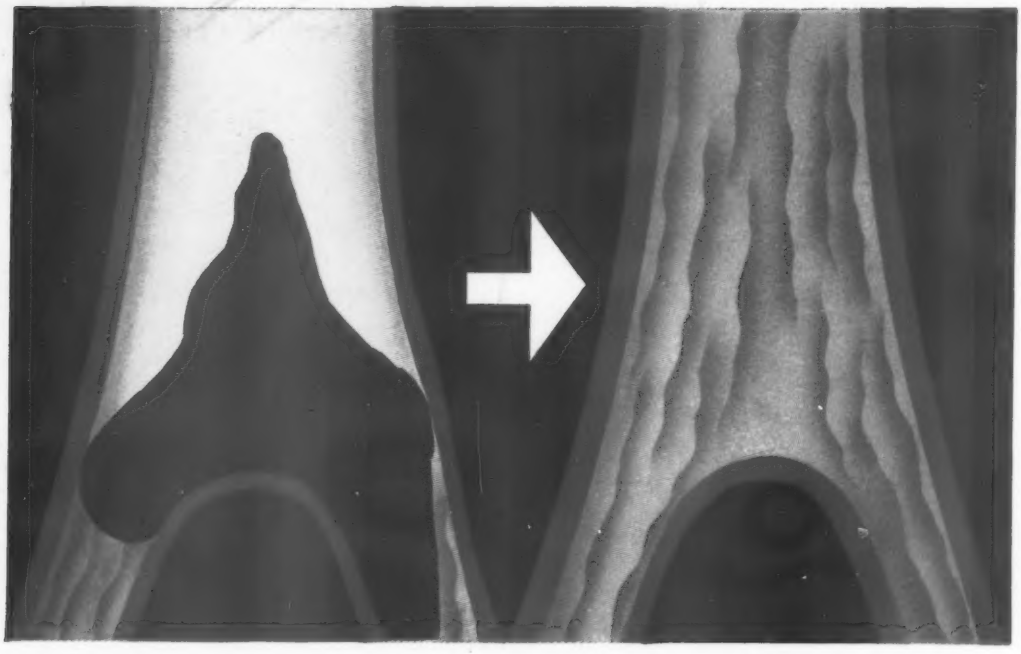

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*Klass, A.: Cur. Therap. Res. 2:322 (July) 1960.

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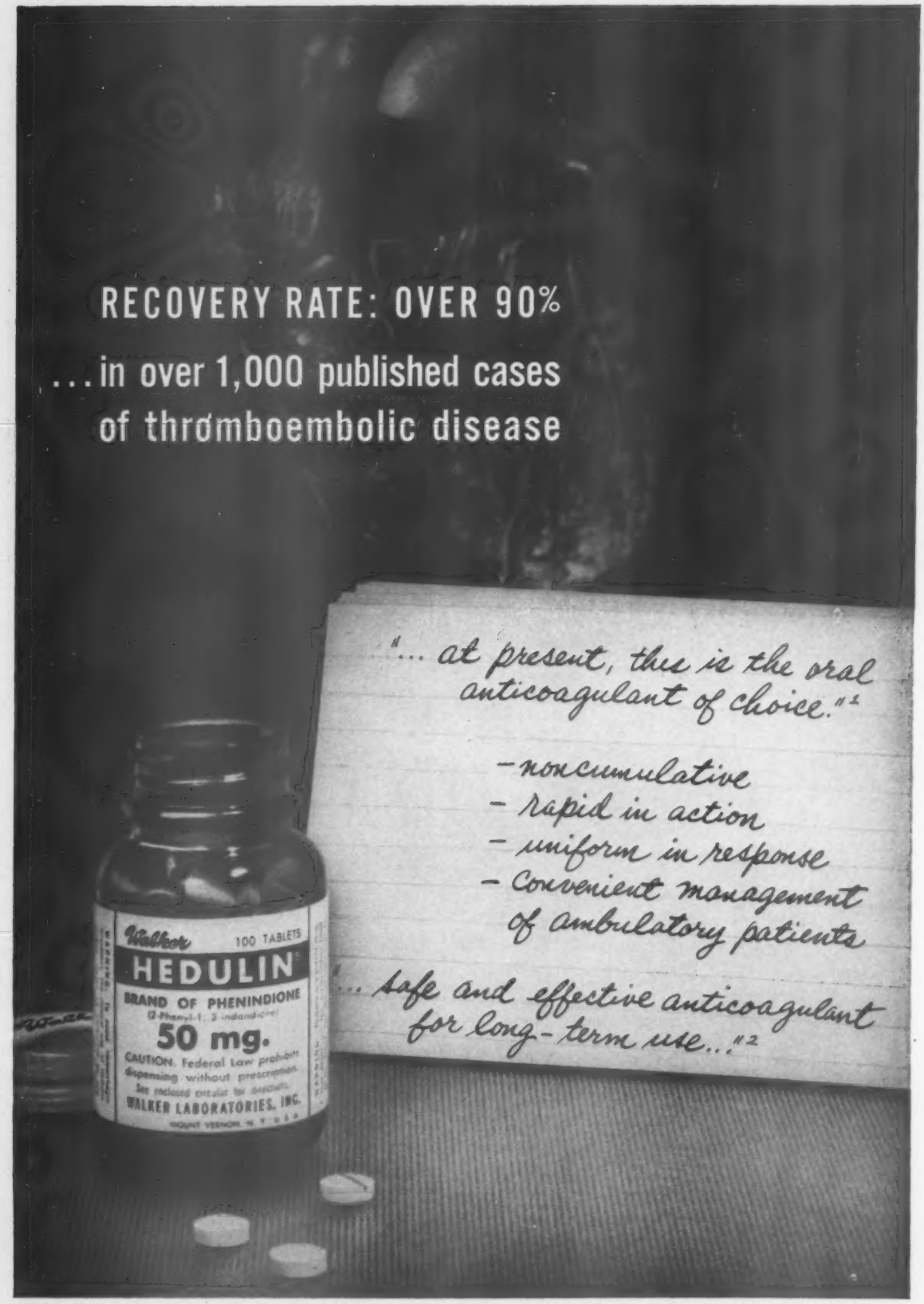
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1. Breneman, G. M., and Priest, E. McC.: Am. Heart J. 50:129 (July) 1955. 2. Tandowsky, R. M.: Am. J. Cardiol. 3:551 (April) 1959.

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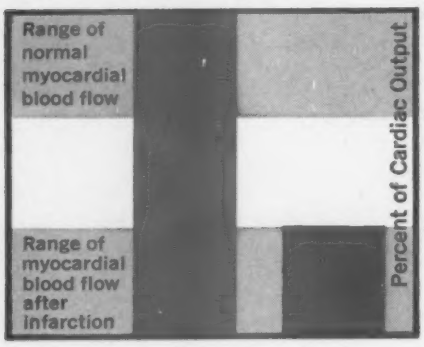

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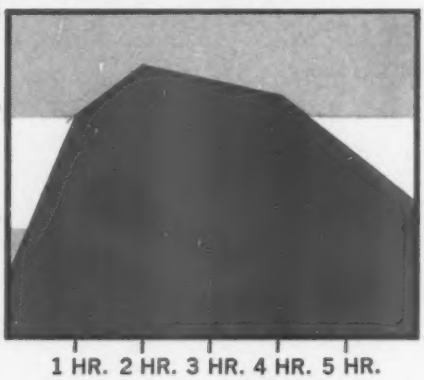

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Volume VII FEBRUARY 1961 Number 2

CONTENTS

Editorial

Balm for Writer's Itch 161
HENRY J. L. MARRIOTT

Clinical Studies

Selective Angiocardiography in the Diagnosis of Atrial Septal Defect (Ostium Secundum Type) 167
EDUARDO COELHO, EDUARDO DE PAIVA AND AMERICO NUNES

Experience with twenty cases of atrial septal defect (ostium secundum type) supports the value of selective angiocardiography in differentiating this defect from ostium primum and in establishing the size of the lesion.

Intracardiac Myxomas and Thrombi. Clinical Manifestations, Pathology and Treatment 176
CRAWFORD W. ADAMS, HAROLD A. COLLINS, ELDON S. DUMMIT AND JOSEPH H. ALLEN

Intracavity cardiac tumors or thrombi, rarely diagnosed before death, should be considered in cardiac patients whose signs and symptoms shift with position or suggest obstructive lesions. Angiocardiography is the most important single diagnostic tool to identify intracavity cardiac tumors.

Blood Gas Changes Following Priscoline Administration in Mitral Stenosis and Chronic Lung Diseases 188
S. STERN AND KARL BRAUN

In patients with mitral stenosis and chronic pulmonary disease Priscoline® injected intravenously lowered the arterial blood oxygen content, probably by increasing the perfusion of poorly ventilated areas in the lungs or increasing the flow through true intrapulmonary shunt vessels, or both.

A Ballistocardiographic Study of Left Bundle Branch Block 192
ARTHUR J. MOSS

Ultra-low frequency acceleration ballistocardiograms on ten patients with left bundle branch block showed a prominent interruption (I^+ deflection) in the early systolic portion of the ballistocardiographic complex due to the delayed onset of left ventricular ejection. An abnormal pattern indicative of accelerated cardiovascular aging present in eight subjects was attributed to associated coronary artery disease, producing altered myocardial function.

Observations on Coronary Sinus Rhythm and Its Mechanism 198
DAVID H. SPODICK AND ROBERT COLMAN

Coronary sinus rhythm, characterized by retrograde atrial activation and normal A-V conduction time, is a transient phenomenon arising from a low atrial focus rather than an upper nodal focus.

Contents continued on page 7

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CONTENTS continued—February 1961

VOLUME SEVEN NUMBER TWO

Adams-Stokes Syndrome during Normal Sinus Rhythm and Transient Heart Block. III. The Paradoxical Effects of Carotid Sinus Digital Pressure and Deep Breathing on Patients with Adams-Stokes Seizures during Normal Sinus Rhythm and Transient Heart Block 204
SIDNEY P. SCHWARTZ AND LEWIS S. SCHWARTZ

In patients with transient heart block who were subject to Adams-Stokes seizures, carotid sinus pressure or deep breathing applied during sinus rhythm produced transitory heart block. On the other hand, the same maneuver during 2:1 A-V heart block caused sinus rhythm, presumably due to improved A-V conduction and other compensatory changes.

Experimental Studies

Study of the Transmembrane Action Potential, Electrogram, Electrocardiogram and Vectorcardiogram of Rats with Left Ventricular Hypertrophy 211
HERMAN UHLEY WITH THE TECHNICAL ASSISTANCE OF JOHN PROCTOR

Augmented QRS voltages in the electrocardiograms of hypertensive rats with hypertrophied hearts result primarily from the increased muscle mass rather than any increased magnitude of the single cell voltage generated by the hypertrophied heart.

Hemodynamic Effects of Balloon Obstruction of the Abdominal Aorta and Superior Vena Caval-Distal Aortic Shunting in Dogs with Myocardial Infarction and Shock 218
LESLIE A. KUHN, FRANK L. GRUBER AND ALBERT FRANKEL

Using balloon catheters to obstruct the abdominal aorta in dogs with coronary shock, the investigators mechanically increased the systemic vascular resistance and the coronary perfusion pressure without significantly raising the right atrial and left ventricular diastolic pressures or calculated left ventricular work.

Physiologic Principles of Partial Extracorporeal Circulation for Mechanical Assistance to the Failing Heart 227
PIERRE M. GALLETTI

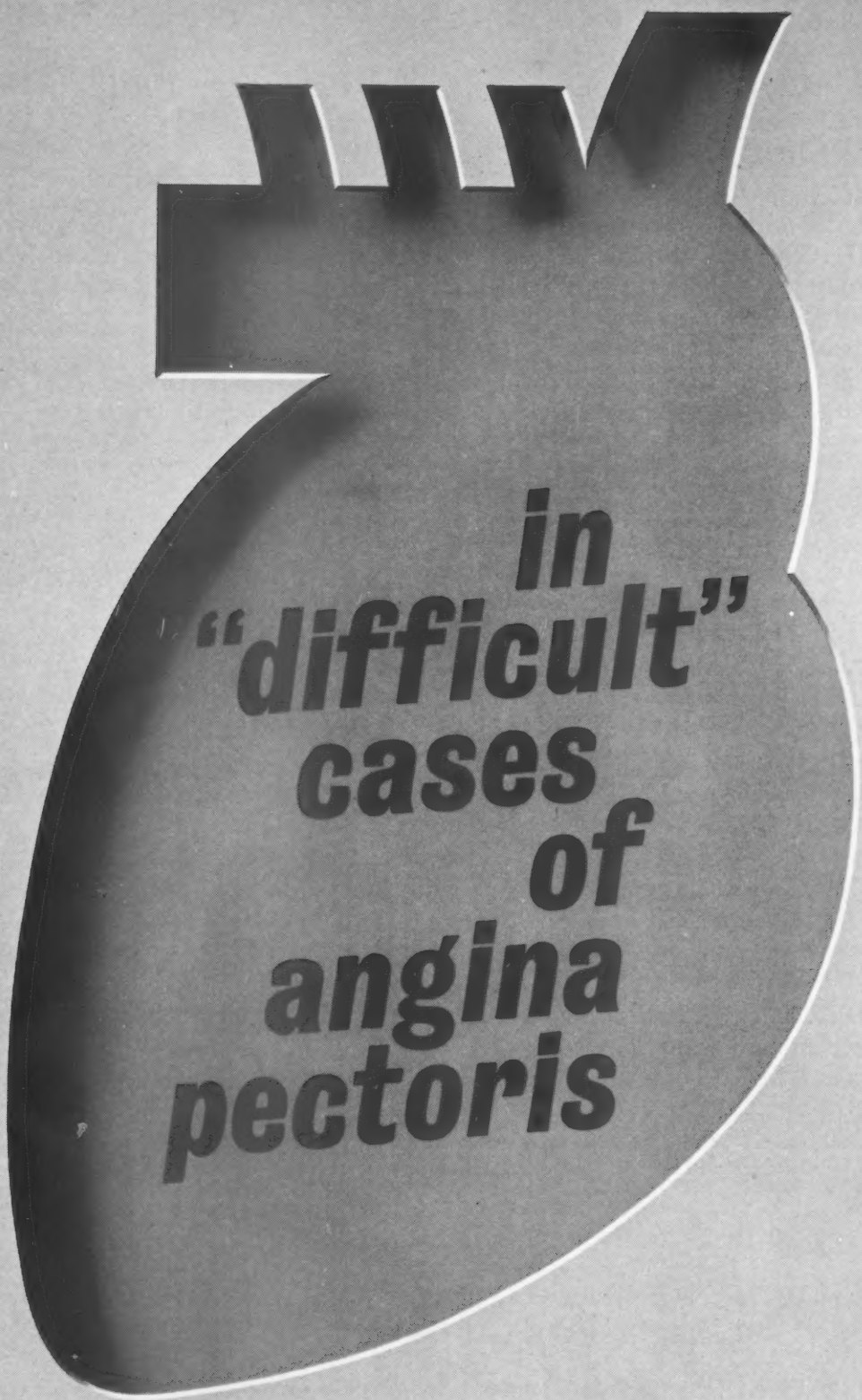
Studies of partial heart-lung bypass indicate that an accurate knowledge of the systemic blood volume is necessary to control the distribution of blood flow between the intracorporeal and extracorporeal circuits. The systemic blood content also influences the pulmonary ventilation.

Review

Two Step Exercise Test as a Test of Cardiac Function in Chronic Rheumatic Heart Disease and in Arteriosclerotic Heart Diasease with Old Myocardial Infarction 234
HERMAN K. HELLERSTEIN, GEORGE B. PROZAN, IRVING M. LIEBOW, ALLEN E. DOAN AND JACK A. HENDERSON

Results of the electrocardiographic two step exercise tolerance test and the Flack test in ninety-two patients with rheumatic heart disease and in 100 patients with arteriosclerotic heart disease suggest that these tests are valuable objective measures of circulatory fitness. The investigators challenge the belief that the abnormal electrocardiographic changes after exercise are either diagnostic of coronary arteriosclerosis or caused solely by an insufficient blood supply to the myocardium.

Contents continued on page 9



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References: 1. W. Hollander and R. W. Wilkins, in J. H. Moyer, Ed., Hypertension, Philadelphia, W. B. Saunders Co., 1959, p. 399. 2. R. W. Oblath, paper read at American Therapeutic Society, 60th Annual Meeting, Atlantic City, N. J., June 6, 1959. 3. N. Bloom, **Virginia M. Month.**, 87:23, 1960. 4. T. Winsor and P. Zarco, **Angiology**, 11: (Part 2), 67, 1960. 5. G. C. Griffith, **Clin. Med.**, 6:1555, 1959. 6. G. C. Griffith, **Dis. Nerv. System**, 21 (Suppl.), 101, 1960.

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CONTENTS continued—February 1961

VOLUME SEVEN NUMBER TWO

Historical Milestones

Right-Sided Ulcerative Endocarditis Recognized Ante Mortem (Charcot and Vulpian, 1862) 253
SAUL JARCHO

An instructive demonstration of the art of conscientious medical examinations.

Case Reports

Congenital Aortic Stenosis in Siblings 262
FRITZ MAINZER AND GAMAL E. MASSOUD

Besides reporting two siblings with congenital aortic stenosis, this paper reviews the familial incidence of congenital heart disease. The incidence of congenital heart disease in subsequent offspring of parents with one child born with a cardiac malformation is 1.8 per cent, six times the expectation of the general population (0.32 per cent).

Patent Ductus Arteriosus in Identical Twins 270
ROGER J. BOULAY

Although patent ductus arteriosus is not rare, its occurrence in both monozygotic twins merits reporting.

Ventricular Septal Defect with Aortic Insufficiency, Acute Rheumatic Carditis and Asian Influenza 273
SHLOMO Z. ROSENBERG AND KARL BRAUN

Asian influenza precipitated pulmonary edema and caused the death of a patient with ventricular septal defect with aortic insufficiency and acute rheumatic endomyocarditis.

Acquired Interventricular Septal Defects Due to Myocardial Infarction and Nonpenetrating Trauma to the Chest 277
PAUL RUBENSTEIN AND DAVID C. LEVINSON

Increasing proficiency in open heart surgery enhances the repair of acquired interventricular septal defects following myocardial infarction or nonpenetrating trauma to the chest wall. Clinical and hemodynamic changes in this type of lesion are described.

Myocardial Infarction Following Penetrating Wounds of the Heart 283
EDWARD J. HEITZMAN AND GEORGE C. HEITZMAN

Electrocardiograms in a case of a self-inflicted knife wound of the heart and chest showed a recent myocardial infarction, probably due to complete severance of a coronary artery.

Myocardial Infarction Following Steroid Therapy in Periarteritis Nodosa . . . 288
RALPH L. NACHMAN

Steroid administration is believed to have produced a clinically silent myocardial infarction in a thirty-four year old man with periarteritis nodosa.

Myxedema Heart Disease and Rheumatic Heart Disease 292
CHARLES A. WHITE

Although rheumatic heart disease and thyrotoxicosis frequently co-exist, rheumatic heart disease and spontaneously occurring myxedema heart disease rarely occur in the same individual. Such a case is described in this paper.

Contents continued on page 11

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CONTENTS continued—February 1961

Pelvic Vein Thrombosis with Pulmonary Vascular Lesions Simulating Primary Pulmonary Hypertension 297
JOSEPH K. FREILICH AND JAN SZATKOWSKI

After left and right heart catheterization a thirty-seven year old woman was considered to have primary pulmonary hypertension, but subsequent autopsy showed extensive pulmonary vascular disease and pelvic vein thrombosis. This case emphasizes the difficulties of diagnosing primary pulmonary hypertension during life.

Diagnostic Shelf

A-V Dissociation with Interference in Transient A-V Block and Left Bundle Branch Block 302
CARLO CANELLA

An interesting arrhythmia in a patient with a past history of diphtheritic myocarditis.

Special Departments

Workmen's Compensation for the Cardiac 305
Progress Notes in Cardiology 307
Book Reviews 309
College News 312
Announcements 314

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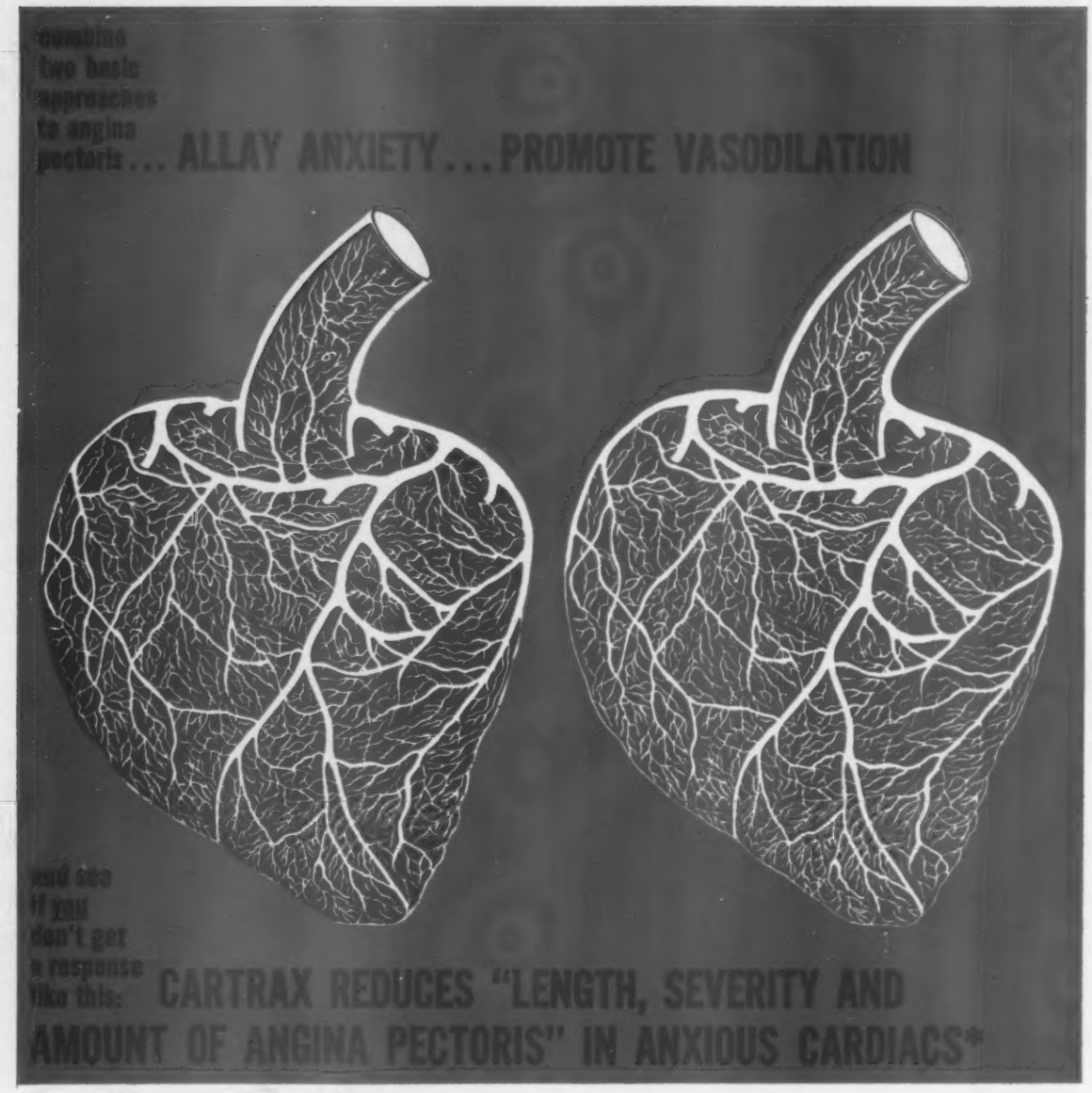
Index to Advertisers on page 55 and 56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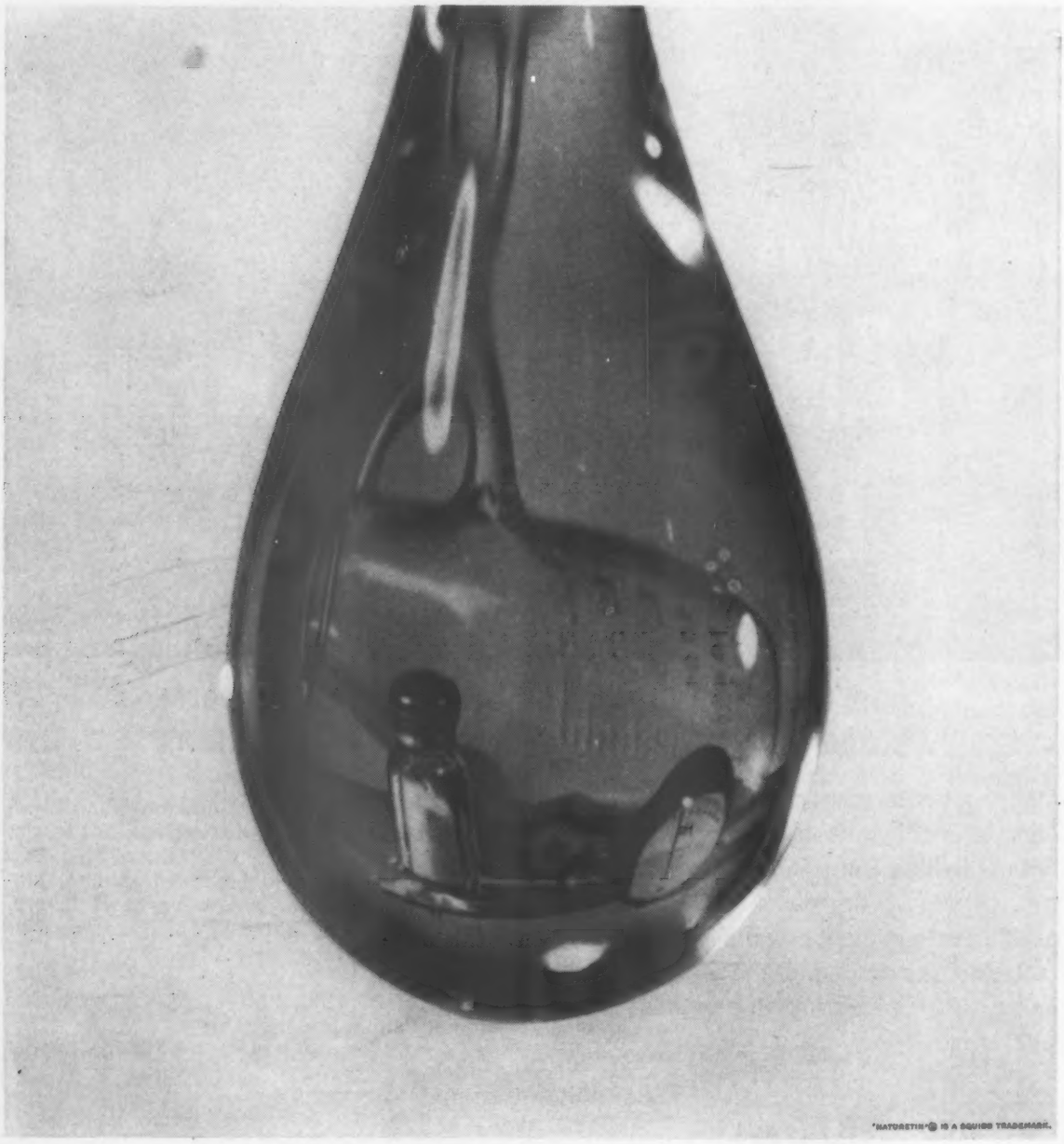

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NEW THOMAS BOOKS FOR THE CARDIOLOGIST

CHEMISTRY AND THERAPY OF CHRONIC CARDIOVASCULAR DISEASE

by **Richard J. Jones** and **Louis Cohen,** *both of University of Chicago.* Any physician who treats patients with heart disease can benefit from the information presented here. The authors review the chemical basis for the pathogenesis and therapy of **three common complications of much chronic cardiovascular disease**—congestive heart failure, thrombosis, and arteriosclerosis. They emphasize the rationale of anticoagulant therapy and the pathogenesis of atherosclerosis. Recent tentative therapeutic efforts directed against an elevated serum cholesterol are outlined. The chemistry of the cardiac glycosides is brought up to date, and the chemistry as well as the mode of action of the new diuretics is presented. An important chapter is devoted to the value of long-term anticoagulant therapy as derived from the personal experience of the authors. *Pub. March '61* (*Amer. Lec. Living Chemistry*)

THE TREATMENT OF HYPERTENSION

by **Sir George White Pickering,** *Univ. of Oxford;* **William Ian Cranston,** *Radcliffe Infirmary, Oxford; and* **Michael Andrew Pears,** *Radcliffe Infirmary, Oxford.* This distinguished contribution adds greatly to the stature of the new, exciting American Lectures in Living Chemistry. The authors unravel the underlying basis of the hemodynamic changes despite the diversity of human factors—some of which are exaggerations of physiologic mechanisms and others definitely abnormal states. **They provide crucial criteria for clinical differentiation between benign and malignant states.** They formulate successful chemotherapy with moderate sustained action of marked intermittent effect for preventing cardiovascular disease and prolonging comfortable living. They integrate experimental knowledge with clinical wisdom in the cause of the hypertensive patient and his everyday problems. *Pub. Feb. '61, 192 pp., 70 il., $7.00* (*Amer. Lec. Living Chemistry*)

THE PLURICAUSAL CARDIOPATHIES (*1961 Beaumont Lecture*)

by **Hans Selye.** Dr. Selye, the brilliant medical scientist whose books and papers have been translated into six languages, has been concentrating for several years on cardiac failures. The publisher is justifiably proud to have scheduled for publication in the spring of 1961 Dr. Selye's latest work for clinical and experimental cardiologists. It is a TEXT that surveys and analyzes the voluminous and often inaccessible polyglot publications now scattered throughout the world literature (520 references)... **an ATLAS illustrating the diverse forms of pluricausal cardiopathies with 278 photographs and drawings**...a SYNOPSIS OF ORIGINAL OBSERVATIONS that does not merely discuss in general terms but actually tabulates basic data upon which the entire concept of pluricausal cardiopathies is based...and a LABORATORY MANUAL that describes in detail all the techniques now routinely used by the author for the production and prevention of the pluricausal cardiopathies. *Pub. May '61*

CARDIACS AND DIABETICS IN INDUSTRY: A Study in Work Experience

by **Grace Wyshak,** Leonid S. Snegireff, *and* Augusta F. Law, *all of Gerontology and Chronic Disease Unit, Harvard School of Public Health.* Presenting the FIRST TRULY OBJECTIVE STUDY comparing the work experience of 709 persons with cardiovascular disease or diabetes with that of 709 matched controls who were free from these diseases. Subjects for study were engaged in a variety of occupations—ranging from sedentary and light work to heavy manual labor. Comparisons of work experience were made by means of intensive study of absence, utilization of medical department facilities, sick benefits and Workmen's Compensation. The data are in agreement with the assertions of many private and industrial physicians that cardiacs can and should work. Results of this study are invaluable in terms of rehabilitating the individual afflicted with heart disease. *Pub. April '61*

CHARLES C THOMAS • PUBLISHER

301-327 East Lawrence Avenue **Springfield, Illinois**

let's stop playing fast and loose with linoleic acid

There seems to be no doubt that *linoleic acid is the key factor* in dietary reduction of serum cholesterol. To reduce serum cholesterol, linoleic acid, the principal *poly*unsaturated fatty acid in edible vegetable fats, must *replace* some of the saturated and *mono*unsaturated fatty acids in the diet, not merely be added to the total intake.

This concept is clearly stated in the following quotation from a recent JAMA editorial: "It is accepted generally that specific alteration in the diet will lower the concentration of cholesterol in the blood. The most effective results to date have been achieved by increasing consumption of polyunsaturated fatty acids, particularly linoleic acid." "A particular regimen will be effective only if polyunsaturated fatty acids are responsible for an appreciable percentage of the total fat calories. That is, they must replace rather than supplement some of the saturated fats and oils already in the diet."[1]

In spite of this clear and unbiased statement, the advertising of some margarines seems designed to mislead physicians and their patients by capitalizing on the publicity given to corn oil as the principal source of linoleic acid. The following ambiguous claims are typical:

According to the headline:

The margarine is made of 100% Corn Oil. Buried in the body copy are the words partially hydrogenated.

Misleading because:

The partial hydrogenation has largely converted linoleic acid into saturated fats and into monounsaturated oleic acid, which has been observed to have no effect on serum cholesterol.

According to the headline:

Some claim to have twice the corn oil nutritional benefit of any other leading spread.

Misleading because:

Such a statement obviously implies that this margarine has twice as much linoleic acid, hence greater cholesterol-lowering effect. The truth is that you can buy a margarine with significantly higher linoleic acid content in drugstores.

And so it goes. Literature sent to physicians and journal ads to the profession have been equally misleading. For example, *references being cited refer to clinical studies with a totally different product.* No wonder the author of the editorial cited above felt compelled to warn physicians about "widespread misinformation in this field!"

We don't like such misleading advertising, and we don't use it to promote Emdee Margarine. We're content to deal in facts:

- **Emdee Margarine contains significantly more linoleic acid than other corn oil margarines currently marketed—and contains significantly less of the unnatural trans isomer forms of fatty acids.**
- **Emdee Margarine—and only Emdee Margarine—was used in clinical evaluation studies, even though others now cite the references.**
- **Emdee Margarine—and only Emdee Margarine—has published reports of its value in cholesterol-lowering diets, including articles in JAMA[2], Geriatrics[3], and American Journal of Clinical Nutrition[4].**

Corn oil margarines are *not* alike. They vary greatly in percentage of the active ingredient—linoleic acid. Of them all, Emdee Margarine has far more linoleic acid. It's true that our patented linoleic acid-sparing process makes Emdee Margarine more expensive. But, it's *worth more* when you want your patient's serum cholesterol to go down.

Although the misleading promotion of some margarines may confuse some of your patients, we feel certain that it will not deceive the critical physician —and that you will continue to depend, as you always have, on the facts and on your own clinical evaluation of your patient's needs.

PITMAN-MOORE COMPANY
DIVISION OF ALLIED LABORATORIES, INC., INDIANAPOLIS 6, INDIANA

EMDEE®
margarine

References: 1. Pollack, H.: J.A.M.A. *172*:1165 (Mar. 12) 1960. 2. Boyer, P. A.; Lowe, J. G.; Gardier, R. W., and Ralston, J. D.: J.A.M.A. *170*:257 (May 16) 1959. 3. Terman, L. A.: Geriatrics *14*:111 (Feb.) 1959. 4. Jolliffe, N.; Rinzler, S. H., and Archer, M.: Am. J. Clin. Nutrition *7*:451 (July-Aug.) 1959.

special process protected by U. S. Patent No. 2,890,959

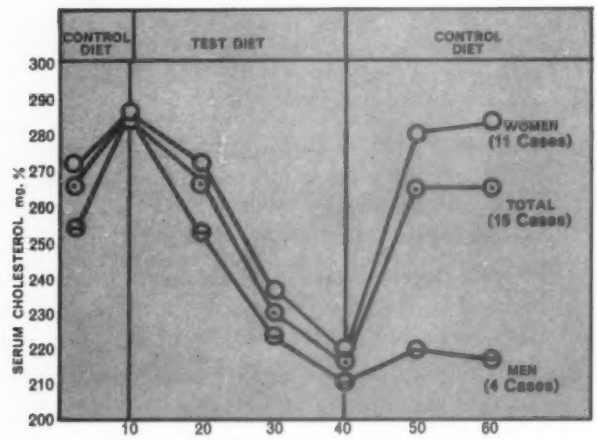
(SEE OTHER SIDE FOR ADDITIONAL INFORMATION ON EMDEE MARGARINE)

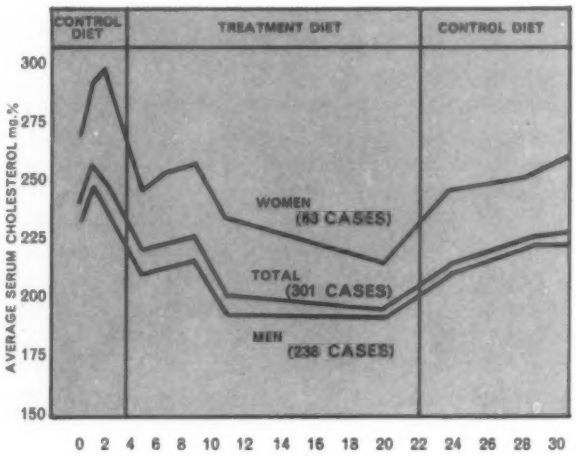
Corn oil margarines are *not* alike in linoleic acid content and, therefore cannot all be of equal value in lowering serum cholesterol. Emdee Margarine contains *significantly more linoleic acid* than any other corn oil margarine currently marketed. Emdee Margarine is the *only* margarine with published scientific reports of its value in reducing serum cholesterol.

Serum cholesterol goes down

when Emdee Margarine is substituted for spreads and shortenings containing more saturated or hydrogenated fatty acids.

Emdee Margarine in place of other spreads and shortenings has been shown to be a practical way to lower serum cholesterol without complicating or creating a weight reduction problem. Emdee provides effective levels of linoleic acid. In clinical studies, patients accepted Emdee Margarine without reservation. Results of these studies indicate Emdee's effectiveness:





"Average serum cholesterol values were noticeably reduced during the test diet, becoming statistically significant at the end of the second ten-day period and showing increasing significance at the end of the third ten-day period."[1]

"In a nine-month study of over 300 inpatients in a state institution, it was found that a regimen employing a nonhydrogenated corn oil margarine (Emdee Margarine) for other solid fats as the principal dietary alteration was effective in achieving and maintaining a reduction in blood cholesterol levels."[2]

References: 1. Terman, L. A.: Geriatrics *14*:111 (Feb.) 1959. 2. Boyer, P. A.; Lowe, J. G.; Gardier, R. W., and Ralston, J. D.: J.A.M.A. *170*:257 (May 16) 1959.

When You Want to Lower Blood Cholesterol

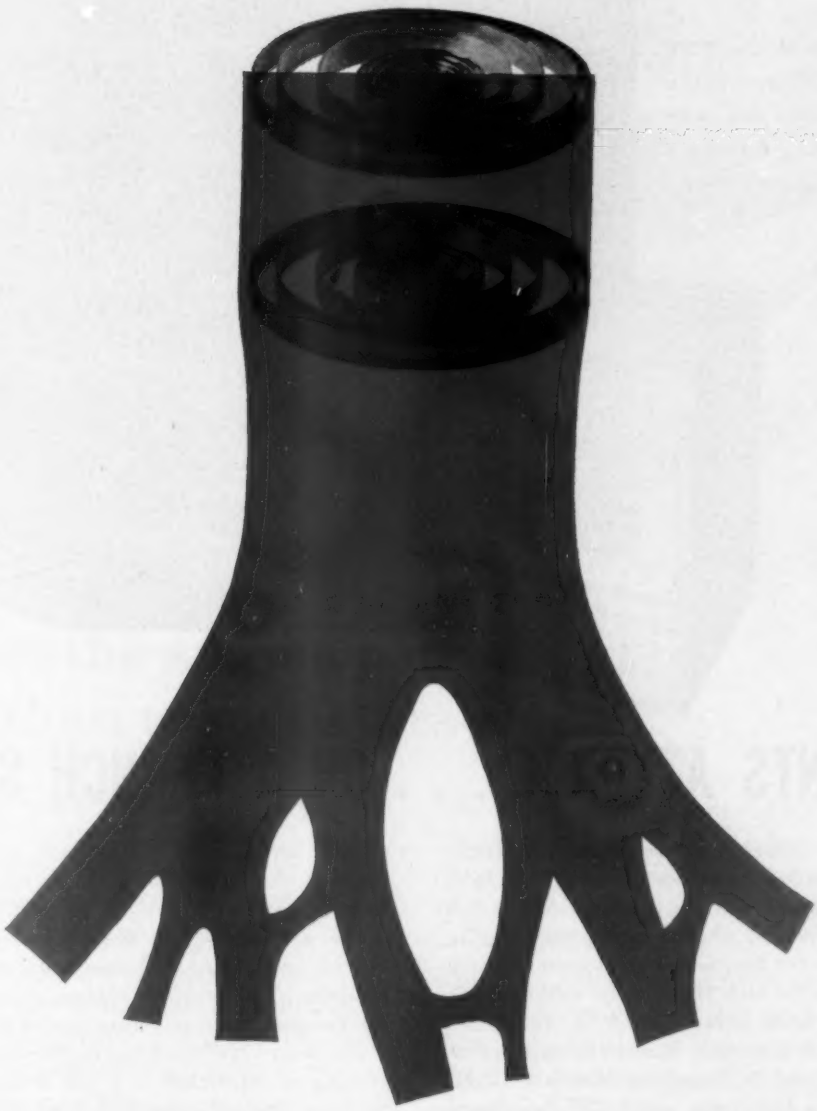
EMDEE®
margarine

PITMAN-MOORE COMPANY
DIVISION OF ALLIED LABORATORIES, INC., INDIANAPOLIS 6, INDIANA

To protect flavor and texture, Emdee Margarine is packaged in cans and kept under constant refrigeration. The linoleic acid-sparing manufacturing process is covered by U. S. Patent No. 2,890,959.

Hygroton®
brand of chlorthalidone

in hypertension and edema, longer in action smoother in effect



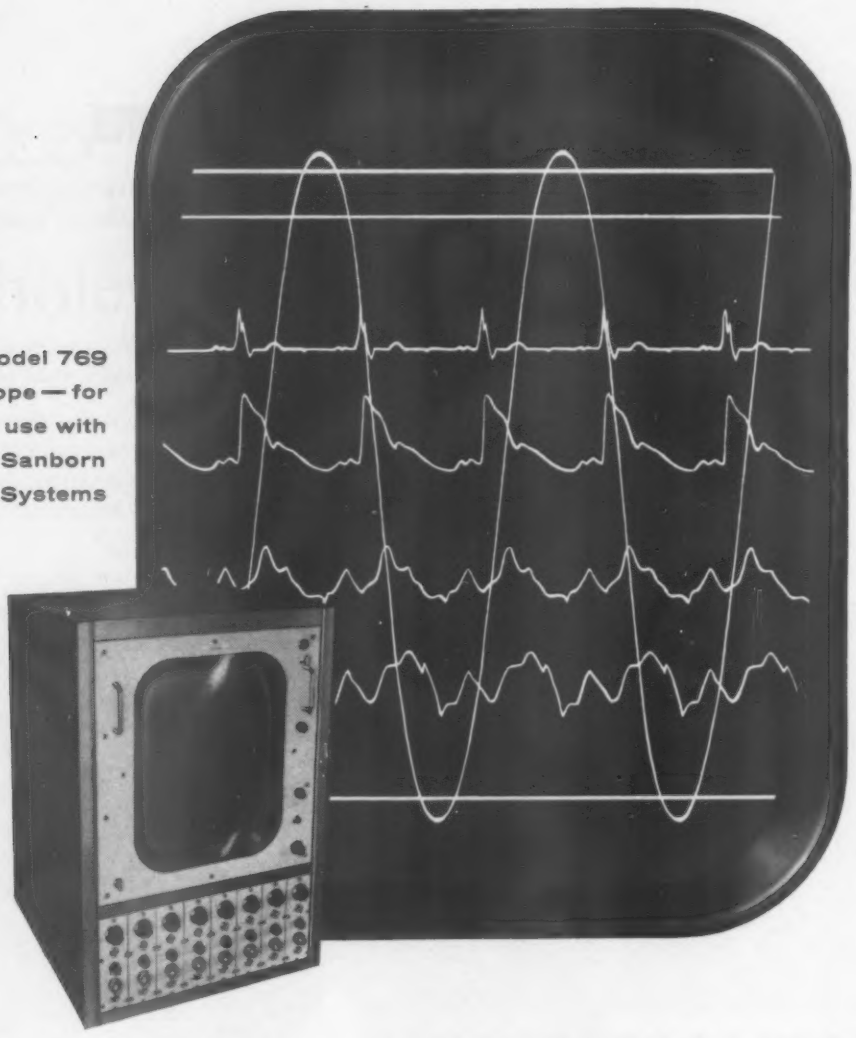
Longer action[1] provides smooth, evenly-sustained therapeutic effect.[2] ■ Potent antihypertensive properties facilitate effective treatment of hypertension, frequently without auxiliary agents.[3] ■ Safeguards against significant potassium loss.[4] ■ Intensity of saluretic action enables liberalization of dietary salt restriction.[3] ■ Simplified dosage schedule affords economy of maintenance on just 3 doses per week.[2]

References: 1. Ford, R. V.: Current Therap. Research 2:347, 1960. 2. Fuchs, M., and others: Current Therap. Research 2:11, 1960. 3. Ford, R. V.: Connecticut Med. 24:704-707, (Nov.) 1960. 4. Ford, R. V.: Texas State J. Med. 56:343, 1960.

Detailed literature available on request.

Hygroton®, brand of chlorthalidone, is available as white, single-scored tablets of 100 mg.

Geigy Pharmaceuticals, Division of Geigy Chemical Corporation, Ardsley, New York HY573-61 Geigy



Sanborn Model 769 Viso-Scope — for monitor use with existing Sanborn Recording Systems

8 EVENTS AT ONCE . . . ON A 17 INCH SCREEN

THE vertically mounted 17″ screen provides ample space for up to 8 clear, long-persistance traces to be shown simultaneously on the Sanborn Model 769 Viso-Scope. Individual plug-in gating amplifiers in the 769 perform the function of an electronic switch — one amplifier for each signal to be shown on the 'scope — the signals being derived by direct connection of the 769 to existing Sanborn Recording Systems such as Model 60 Twin-Viso, Models 64, 77M, 150M and 350M Poly-Visos, and 550M Poly-Beam.

Automatic or manual trace sweep speeds of 2, 4 and 8 seconds (5, 2.5, and 1.25 inches/sec) are provided and an additional manual sweep speed of 25 seconds is included for use when slowly changing waveforms such as dye dilution curves are studied.

Controls permit sensitivity ranges from 5″/volt to ⅛″ per volt, positioning of each signal at any level on the screen, and vector loop presentation. A Polaroid filter is used to minimize interference from room lighting, and provision is made for tilting the 'scope unit forward (up to 20 degrees) for optimum viewing ease. Front and rear input connections are available. With suitable cabling, several 769 units can be connected together for master slave operation.

The Model 769 Viso-Scope — scheduled for delivery starting in September — is the first of a group of Sanborn "760" Monitor Units (including low voltage preamplifiers) soon to be made available for use in Hospital Operating Rooms, Recovery Rooms and Intensive Care Units, and by Catheterization Units and Teaching Groups.

For complete details, contact your nearest Sanborn Branch Office or Service Agency, or write the Inquiry Director at the Main Office in Waltham.

SANBORN COMPANY

MEDICAL DIVISION, 175 WYMAN STREET, WALTHAM 54, MASS.

Protects the angina patient better than vasodilators alone

Unless the coronary patient's ever-present anxiety about his condition can be controlled, it can easily induce an anginal attack or, in cases of myocardial infarction, can delay recovery.

This is why Miltrate gives better protection for the heart than vasodilators alone in coronary insufficiency, angina pectoris and postmyocardial infarction.

Miltrate contains PETN (pentaerythritol tetranitrate), acknowledged as basic therapy for long-acting vasodilation. . . .

What is more important—Miltrate provides Miltown, a tranquilizer which, unlike phenobarbital, relieves tension in the apprehensive angina patient without inducing daytime fogginess.

Thus, your patient's cardiac reserve is protected against his fear and concern about his condition; his operative arteries are dilated to enhance myocardial blood supply—and he can carry on normal activities more effectively since his mental acuity is unimpaired by barbiturates.

REFERENCES: 1. Ellis, L. B. *et al.:* Circulation *17*:945, May 1958. 2. Friedlander, H. S.: Am. J. Cardiol. *1*:395, Mar. 1958. 3. Riseman, J.E.F.: New England J. Med. *261*:1017, Nov. 12, 1959. 4. Russek, H. I. *et al.:* Circulation *12*:169, Aug. 1955. 5. Russek, H. I.: Am. J. Cardiol. *3*:547, April 1959. 6. Tortora, A. R.: Delaware M. J. *30*:298, Oct. 1958. 7. Waldman, S. and Pelner, L.: Am. Pract. & Digest Treat. *8*:1075, July 1957.

Supplied: Bottles of 50 tablets. Each tablet contains 200 mg. Miltown and 10 mg. pentaerythritol tetranitrate.

Dosage: 1 or 2 tablets q.i.d. *before meals* and at bedtime, according to individual requirements.

CML-3619

Miltrate®

Miltown® (meprobamate) + PETN

WALLACE LABORATORIES / *Cranbury, N. J.*

extends the usefulness of Vitamin K_1 therapy†...

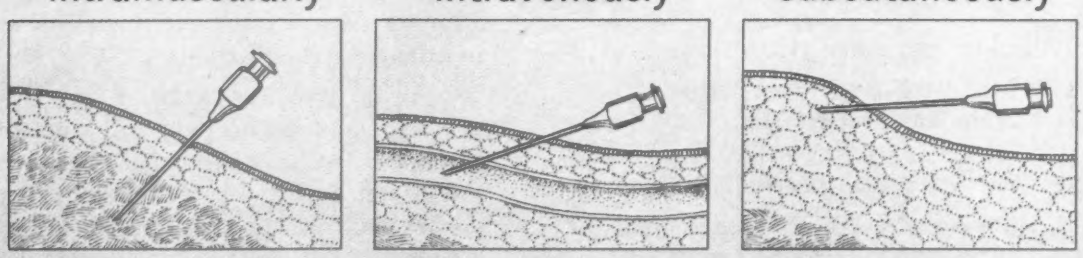
NEW Injection

AquaMEPHYTON

AQUEOUS COLLOIDAL SOLUTION

†a clear, stable, aqueous colloidal solution for administration

• intramuscularly • intravenously • subcutaneously



a dosage form for every Vitamin K indication:

AquaMEPHYTON (for intramuscular, intravenous, subcutaneous administration), 1-cc. ampuls containing 10 mg. MEPHYTON, Vitamin K_1

TABLETS MEPHYTON (for oral administration), 5 mg.

EMULSION MEPHYTON (for intravenous administration only), 1-cc. ampuls containing 10 mg. and 50 mg. per cc.

OF MEPHYTON®, VITAMIN K_1

Vitamin K_1 "has a more prompt, more potent and more prolonged effect than the vitamin K analogues" *

*Council on Drugs: New and Nonofficial Drugs, Philadelphia, J. B. Lippincott Co., 1960, p. 732

reduces the hazard of hemorrhage due to hypoprothrombinemia in:

- prophylaxis and therapy of hemorrhagic disease of the newborn
- surgery, preoperatively and postoperatively
- anticoagulant-induced prothrombin deficiency
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- prothrombin-depressing drugs such as salicylates and phenylbutazone
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For additional information, write Professional Services, Merck Sharp & Dohme, West Point, Pa.

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AquaMEPHYTON AND MEPHYTON ARE TRADEMARKS OF MERCK & CO., Inc.

Introducing new therapy for

hypertension and congestive failure

lowers blood pressure
drains excess water
calms apprehension

Now the most widely prescribed diuretic-antihypertensive, hydrochlorothiazide, is combined with the most widely prescribed tranquilizer, meprobamate. It is called "Miluretic", and constitutes new therapy for hypertension and congestive failure — *especially when emotional factors complicate treatment.*

What does Miluretic do? Both components are of proven value in the management of hypertension. In congestive failure, Miluretic provides smooth, continuous diuresis. But Miluretic's biggest advantage is that it tranquilizes hypertensive and edematous patients safely and quickly—*a boon to the physician whose patients' emotional reaction to their condition complicates therapy.* Unlike Rauwolfia compounds, Miluretic does not cause depression or nasal congestion.

new **Miluretic***

MILTOWN® + HYDROCHLOROTHIAZIDE

Composition: 200 mg. Miltown (meprobamate, Wallace) + 25 mg. hydrochlorothiazide

Dosage: For hypertension, 1 tablet four times a day. For congestive failure, 2 tablets four times a day.

Supplied: Bottles of 50 white, scored tablets

Available at all pharmacies
Write for samples and complete literature to

*Trade-mark
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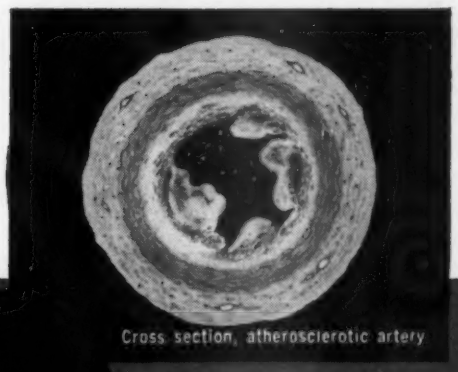
WALLACE LABORATORIES / *Cranbury, N. J.*

outstanding nutritional research achievement



Cross section, atherosclerotic artery

to aid in the dietary control of serum cholesterol

MAZOLA®

MARGARINE
scientifically formulated with pure liquid **non-hydrogenated** MAZOLA Corn Oil.

U.S. Pat. No. 2,955,039

MAZOLA Margarine is an economical tablespread and serves as a solid shortening, rich in linoleates and low in saturates—making it an ideal dietary adjunct in the management of serum cholesterol. It contains 2 to 3 times as much natural linoleic acid as any other margarine readily available in grocery stores from coast to coast, and 5 to 8 times as much as butter. It contains no dairy or animal fats, no coconut oil, and no cholesterol.

MAZOLA Margarine is indistinguishable from other quality margarines as to taste, aroma and handling characteristics. Thus, it can be part of the regular diet for the whole family, including the hypercholesterolemic patient. The major ingredient in MAZOLA Margarine—liquid MAZOLA Corn Oil—is NOT hydrogenated, thereby preserving its rich content of linoleates.

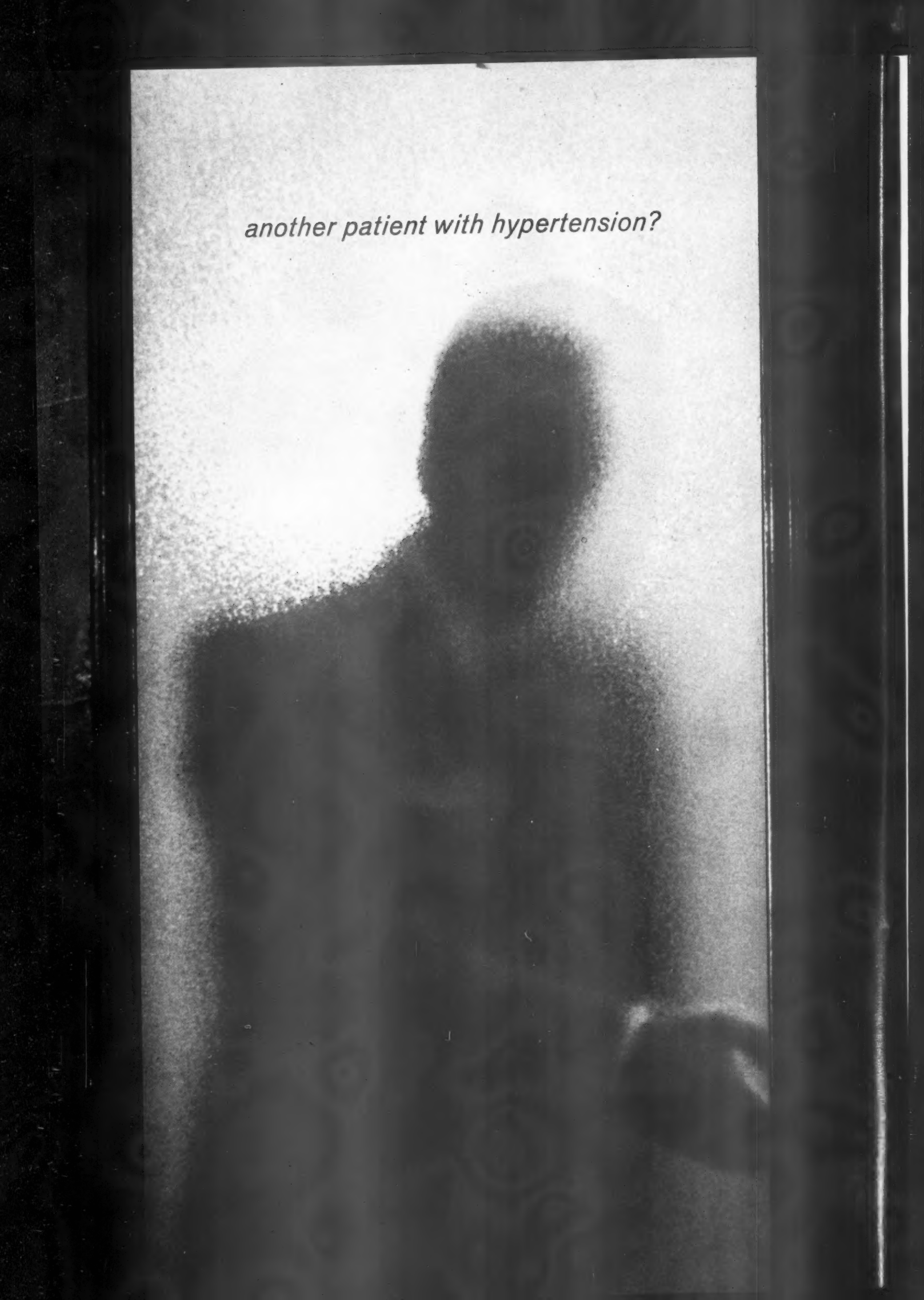
The average daily intake, two ounces or 56.8 Gm. (4 tablespoons) of MAZOLA Margarine, supplies

Linoleic acid	12 Gm.
Oleic acid	23 Gm.
Saturated fatty acids	8 Gm.
Plant sterols (sitosterols)	215 mg.
Natural tocopherols	30 mg.
Vitamin A	1870 USP units
Vitamin D	250 USP units
Calories	415

Available in the refrigerator sections of grocery stores in the same general price range as other premium quality margarines, in 1-lb. packages (four ¼ lb. sticks).

Send for free booklet:
"Recent Advances in the Dietary Control of Hypercholesterolemia."

BEST FOODS • Division of Corn Products Co., NEW YORK 22, N. Y.


another patient with hypertension?

indicated in all degrees of hypertension

effective by itself in most hypertensives

HYDROPRES*

HYDRODIURIL® (HYDROCHLOROTHIAZIDE) **with RESERPINE**

HYDROPRES can be used:

- *alone* (In most patients, HYDROPRES is the only antihypertensive medication needed.)
- *as basic therapy, adding other drugs if necessary* (Should other antihypertensive agents need to be added, they can be given in much lower than usual dosage so that their side effects are often strikingly reduced.)
- *as replacement therapy, in patients now treated with other drugs* (In patients treated with rauwolfia or its derivatives, HYDROPRES can produce a greater antihypertensive effect. Moreover, HYDROPRES is less likely to cause side effects characteristic of rauwolfia, since the required dosage of reserpine is usually less when given in combination with HydroDIURIL than when given alone.)

HYDROPRES-25

25 mg. HydroDIURIL, 0.125 mg. reserpine.
One tablet one to four times a day.

HYDROPRES-50

50 mg. HydroDIURIL, 0.125 mg. reserpine.
One tablet one or two times a day.

also available: **HYDROPRES-Ka-50**

50 mg. HydroDIURIL, 0.125 mg. reserpine, 572 mg. potassium chloride.
One tablet one or two times a day.

If the patient is receiving ganglion blocking drugs or hydralazine, their dosage must be cut in half when HYDROPRES is added.

For additional information, write Professional Services, Merck Sharp & Dohme, West Point, Pa.

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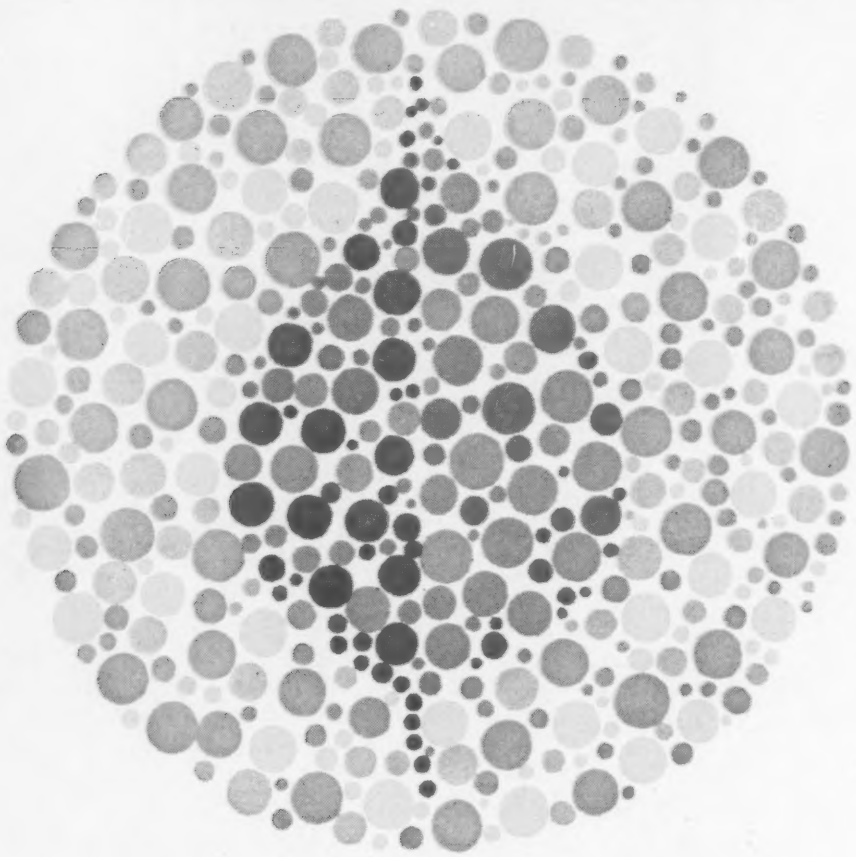
*HYDROPRES, HYDROPRES-Ka, AND HYDRODIURIL ARE TRADEMARKS OF MERCK & CO., INC.

"SEEING YELLOW" ON DIGITALIS LEAF 61-year old male with syphilitic heart disease, cardiac enlargement Grade II, sinus rhythm, right bundle block and aortic insufficiency. Evaluated to be in class III-C. For 11 months, he took 0.1 Gm. of digitalis leaf daily. Admitted to hospital because of nausea, vomiting and disturbance in color-vision. Medication was discontinued for 30 days, after which he was redigitalized with digitoxin and discharged on 0.1 Gm. digitalis leaf daily. Four days later he was readmitted with nausea, vomiting, disturbed color-vision. Digitalis again discontinued for 5 days and toxic symptoms disappeared. Patient then placed on GITALIGIN, 0.5 mg. per day. There were no toxic signs or symptoms and failure was well controlled.[1]

"DIGITALIS TOXICITY IS SEEN WITH INCREASING FREQUENCY TODAY..."[2]



for maximal digitalis activity with minimal toxicity

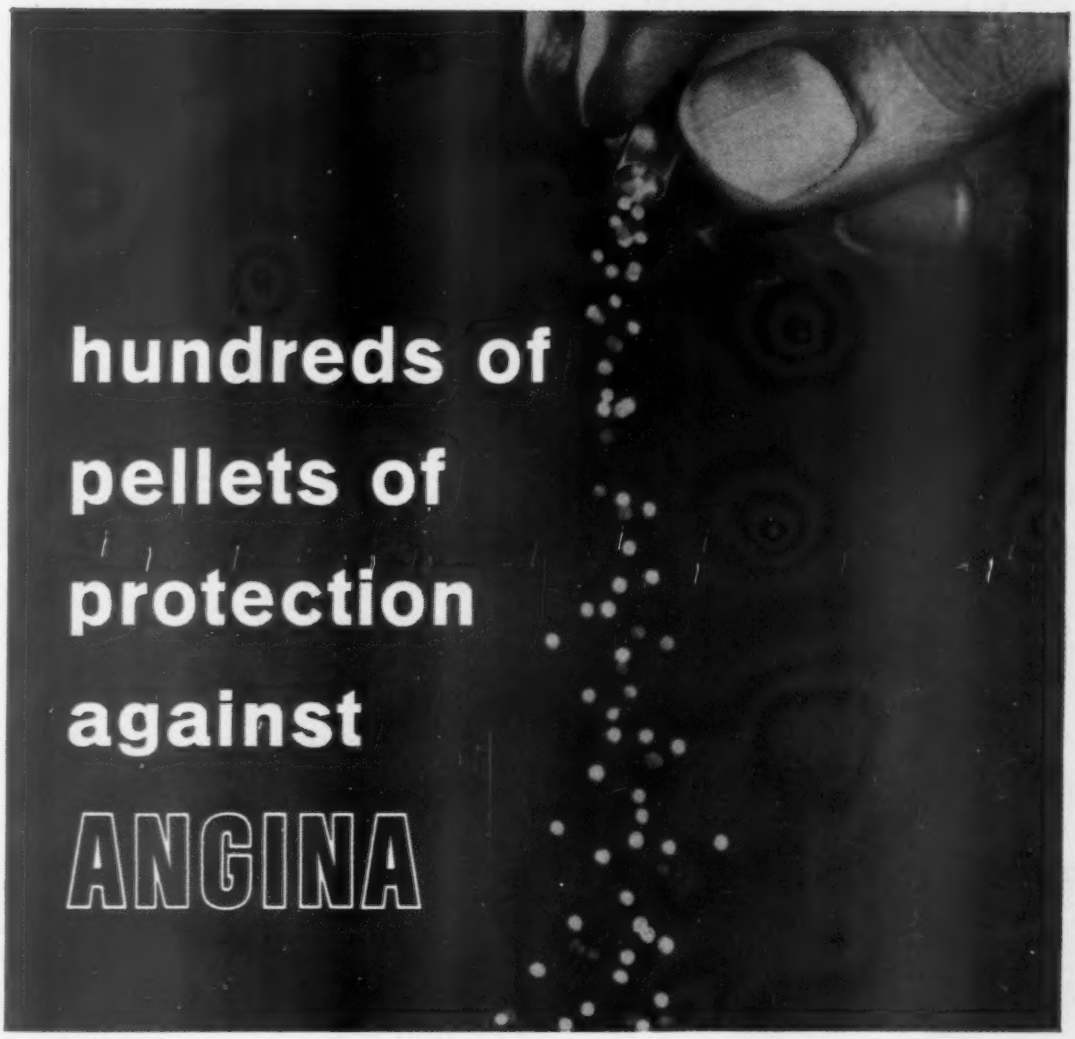
Gitaligin®†

"...patients who became toxic very readily with other agents could later be satisfactorily digitalized with gitalin (GITALIGIN)."[2]
Wider margin of safety—frequently effective in patients refractory to other digitalis glycosides • broader clinical utility—therapeutic dose only ⅓ the toxic dose • faster rate of elimination than digitoxin or digitalis leaf. □ Supplied: 0.5 mg. scored tablets—bottles of 30 and 100.

1 Dimitroff, S P et al.: Ann. Int. Med. 39:1189. 1953 2. Pastor, B. H.: GP 22:85, 1960.

†amorphous gitalin, White

White WHITE LABORATORIES, INC. • Kenilworth, New Jersey



PENTRITOL® TEMPULES

controlled disintegration capsules

A single 30 mg. Pentritol Tempule with 12 hour action exhibits an even nitrite release which "tends to produce a smooth, prolonged response similar to that of the sustained release of modern depot injections."[1] Duration, frequency, and severity of anginal attacks are markedly lessened. Patients showing little progress during years of therapy with 80 mg. daily of PETN tablets, respond favorably to the smaller dose of Pentritol Tempules.[2] Kamil and Klinger report the response of their patients to a timed-disintegration pentaerythritol tetranitrate capsule as excellent, with nitroglycerin requirements reduced as much as 85%.[3]

1. Biegeleisen, H. I.: Clin. Med. *2*:1005, 1955. 2. Roberts, J. T.: Clin. Med. *4*:1375, 1957. 3. Kamil, M., and Klinger, I.: New York State J. Med. *59*:3398, 1959.

PENTRITOL

Each Pentritol Tempule is a controlled disintegration capsule containing 30 mg. of pentaerythritol tetranitrate in granular form. An initial dose of 10 mg. is released at once; a second dose 4 hours later; and a third dose 8 hours after ingestion. Thus, each Tempule affords at least 12 hours of coronary vasodilation. ACTION AND USES: Effective therapy for and prophylaxis against anginal attacks. One Tempule morning and evening will provide 24 hours of effective medication, with a smooth, sustained clinical effect that has shown superior results. Pentritol reduces or eliminates nitroglycerin requirements, stops or reduces frequency of anginal attacks, eliminates or mitigates pain, and increases capacity for physical activity. CONTRAINDICATIONS: Observe caution in glaucoma. DOSAGE: One Pentritol Tempule morning and evening, approximately 12 hours apart. SUPPLIED: Bottles of 60 and 250. Also available: Pentritol®-B Tempules®, with 30 mg. pentaerythritol tetranitrate and 50 mg. butabarbital, for 12 hours of coronary vasodilation plus sedation.

ARMOUR PHARMACEUTICAL COMPANY
KANKAKEE, ILLINOIS • *Armour Means Protection*

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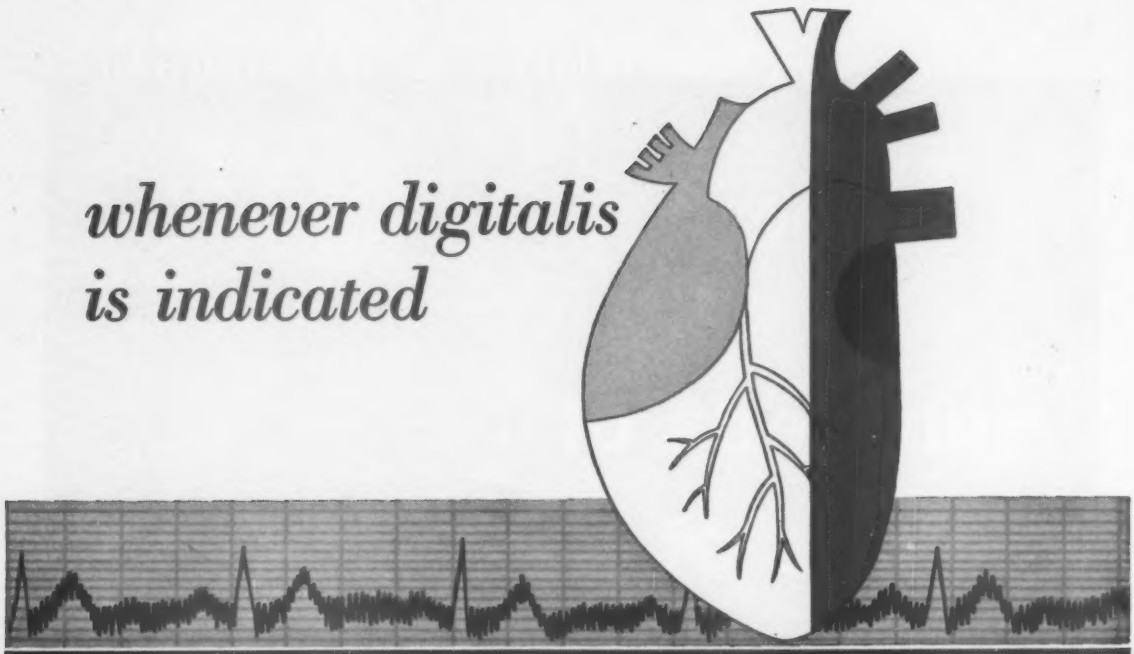
whenever digitalis is indicated



'LANOXIN'® brand DIGOXIN

formerly known as Digoxin 'B. W. & Co.'®

"If one digitalis agent were to be recommended for its adaptability to the many and varied clinical contingencies, we believe Digoxin would be the drug of choice."

Lown, B., and Levine, S. A.: Current Concepts in Digitalis Therapy, Boston, Little, Brown & Company, 1954, p. 23, par. 2.

'LANOXIN' TABLETS
0.25 mg. scored (white)
0.5 mg. scored (green)

'LANOXIN' INJECTION
0.5 mg. in 2 cc. (I.M. or I.V.)

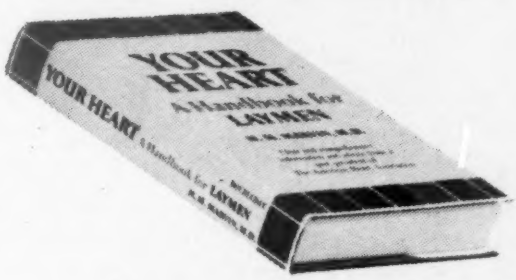
'LANOXIN' ELIXIR PEDIATRIC
0.05 mg. in 1 cc.

BURROUGHS WELLCOME & CO. (U.S.A.) INC., Tuckahoe, N.Y.

AMERICAN HEART ASSOCIATION HOWARD W. BLAKESLEE AWARD

★ 1960 ★

Citation: "YOUR HEART: *A Handbook for Laymen* is judged to be a most valuable contribution to literature designed to improve public understanding of the heart and circulatory diseases. Written with meticulous concern for scientific fact, this book serves the physician, the patient and his family, by presenting the latest advances in treatment and prevention with hope, lucidity, and compassion."



*"Every physician who believes that the patient is a partner in the management of his disease, will welcome this book and hasten to put it into the hands of as many people as possible."**

YOUR HEART

A Handbook for Laymen

by H. M. Marvin, M.D., Associate Clinical Professor of Medicine, Yale University School of Medicine; former President, American Heart Association; former member National Advisory Heart Council (U.S. Public Health Service)

"No doctor need fear that his patient will be unduly alarmed by reading the material here presented or that he will be given anything but sensible advice. In short, Dr. Marvin's new book is heartily recommended."—*N. Y. State Journal of Medicine**

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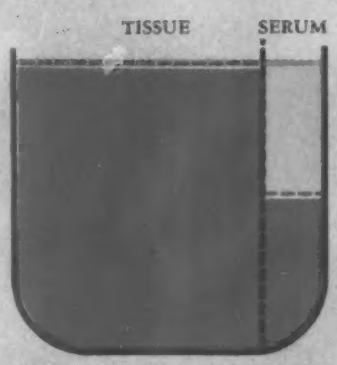
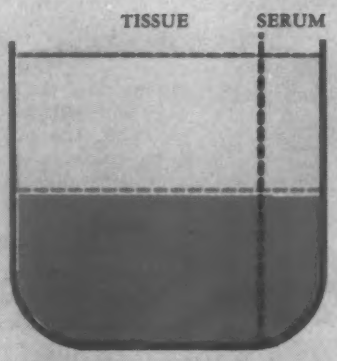


OTHER MEASURES

There is no evidence that tissue cholesterol is reduced even in the face of serum cholesterol reduction.



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The American Journal of Cardiology

VOLUME VII FEBRUARY 1961 NUMBER 2

EDITORIAL

Balm for Writer's Itch

MANY MOTIVES lead to the outpouring of the printed medical word. One is what Juvenal picturesquely called *insanabile scribendi cacoethes*, the incurable itch to write; and indeed it has been well said that nothing can relieve this particular itch except the scratching of a pen. A second is the urge for self advertisement. Mencken has pointed out that, among writers in general, the yearning to make a noise is second only to the yearning to make money. A third motive is the genuine wish to communicate information of value to one's colleagues, or the sense of duty that certain important observations should be recorded. Yet another is what, on the analogy of the physiologist's *vis a tergo*, one may choose to call the *vis a supero*, or the push from above. This is part of the unhappy paradox that department heads stridently insist that their juniors give birth to a stream of publications, yet few allot time in their curriculums for much needed guidance in the gentle art of writing. The unfortunate but not unnatural result is that many of these forced births are literary monsters.

No doubt most of us write because of a varying blend of two or more of these stimuli; but whatever our motives, let us admit the fact that we all have one common aim, to be read. The written word has only one excuse for existence; it is written to be read; unread, it is dead. It is therefore the plain duty of everyone who takes it upon himself to write to make what he writes as readable as he can.

The following paragraphs will be devoted to comments on style and readability. For the present purpose we shall assume that the author has done a worth while piece of original work or at least has something worth saying; that he has acquired the five by eight card habit and has done the necessary library research without relegating his reference work to the tender but misplaced mercy of a willing librarian; that his statistics, if any, are significant and his conclusions valid; and that he has learned the virtue of scissors and pastepot and with their help has marshalled his material in good order. At this stage he must concern himself with the all-important finishing touch. He must now present his material in as palatable a form as possible and phrase his writing so that he conveys exactly what he intends to convey. His style is important because lapses, inaccuracies and ambiguities irritate the reader. "The difficulty is not to write," said Stevenson, "but to write what you mean; not to affect your reader, but to affect him precisely as you wish."

A good writer is made, not born; and any man can improve the style and clarity of his writing by working at it. "What is written without effort," said Samuel Johnson, "is in general read without pleasure"; and Sheridan echoed him, "Easy writing's curst hard reading." It is the writer's challenge to write hard and make it easy reading, for "the heart of style is consideration for the reader and it is not for nothing that style has been defined as good manners in writing."[1] The etiquette of writing has definite rules that anyone can follow.

THINGS TO DO

1. Shorten It: Brevity is the soul of style. Cut out all the deadwood; make sure that every syllable is needed. Strive to earn what was said of Milton's words, "Fewer would not have serv'd the turn and more would have been superfluous." But make no mistake about it, shortening takes time and is hard work: "If I had more time I would write you a shorter letter," said Ben Franklin.

2. Make the Introduction Brief and Make It

Good: Professional writers have a telling formula for putting an article together:

Hey! You! See! So!

First arrest the reader's attention (*Hey!*). Then make it clear why he should be interested in your article (*You!*). Having got him on the hook, belabor him with the facts and fancies you want him to absorb (*See!*); and finally draw the threads together in a logical conclusion (*So!*).

Medical writing obviously cannot be so dramatic or startling as commercial writing. But bear this formula in mind and apply its principles when possible. At least make the introduction brief and by this alone make it attractive. It is often possible to begin with an arresting opening sentence. If the first sentence is brief and breezy, the second is more likely to be read. For example, an article on complete A-V block is less likely to be pursued if the first sentence begins

> "Complete A-V block was first described by Arbuthnot in 1873 during his classical experiments with dogs, when he found that, if the upper part of the interventricular septum was injured by burning or cutting, there was . . ."

than if it runs

> "Complete A-V block is not always as complete as the term implies."

Devote much time to opening sentences and write them last after the rest of the paper has taken shape. As Peter Quince says, "do *not* begin at the beginning."[2]

3. In medias res, which is best translated "into the thick of things," is a catchword of professional writers, borrowed from Horace, reminding them to get on with the job and come quickly to the point. This of course will be the natural consequence of a brief introduction. Then, if the writer has a worth while message, and he shouldn't be writing if he hasn't, let him deliver it while he still has his reader on the hook. Too often the interesting and original message is postponed till a long and ponderous introduction has sapped the reader's enthusiasm.

4. Prefer the Familiar, Concrete, Single, Short, Saxon Word: In medicine we are afflicted with so many foreign polysyllables that it is clearly impossible to avoid them. If we mean spondylolisthesis or gastrojejunostomy, there is nothing else for us to use except an even clumsier paraphrase. This is all the more reason for keeping the cement substance of our writing as clean and simple as possible. We should avoid the far-fetched and unfamiliar, the abstract word, the circumlocution, the long or the Romance word wherever possible. We should use best rather than optimal, thin for asthenic, fat for obese, limb for extremity. We should use verbs and nouns and economize in adjectives and adverbs. We should use transitive verbs and use them in the active voice whenever we can.

5. Vary Sentence Length and Rhythm: One of Elmer Shaw's ten commandments is "Thou shalt not commit monotony." Nothing is more tedious than to read sentence after sentence of about the same length. And although it is bad to write consistently long sentences, it is certainly worse to get in the habit of writing monotonously uniform ones. An occasional long sentence, if well constructed, is stimulating. Paul White has the happy knack of being able to pilot his reader safely through outrageously long sentences and bring him safely and comprehendingly to the other end. Take for example the following from his "Heart Disease":

> "The blood pressure in hypertensive heart disease generally remains high, but sometimes, either because of spontaneous remission or because of heart failure or general vasomotor collapse, and in some cases evidently aided by treatment, it may fall to average normal or nearly normal levels, leaving obscure the cause of the cardiac enlargement and failure unless knowledge exists of the previous hypertension."

A sentence of no less than sixty-one words, yet there is no difficulty in following the logical march of his clauses; this is because he writes simply and clearly and you can follow him even when he forgets to take a breath.

6. Punctuate for the reader, not for the grammarian. Commas are to the reader what comfort-stops are to the motorist.

7. Use Subheadings Freely: Subheadings break monotony and serve as useful signposts to the reader. A sea of unbroken print deters the tired reader.

8. Read it aloud or, preferably, have someone read it to you. If it reads smoothly aloud, it will read elegantly in print. It is better for someone disinterested to read it to you because you unconsciously "baby" your own production and make it sound better than it is; but if you listen to someone else stumbling through it, someone who has no parental regard for your creation, you will readily perceive its congenital blemishes.

9. "*Murder your darlings*" is Quiller-Couch's way of saying that if you are unduly proud of a deft piece of writing, beware of it: "Whenever you feel the impulse to perpetrate a piece of exceptionally fine writing, obey it—wholeheartedly—and delete it before sending your manuscript to press."[3] Putting a line through a sentence that we have fashioned with loving care is something like strangling a daughter and we cannot expect to enjoy it; but we must learn to tolerate with equanimity the profitable pain of the pruning process. (There goes a "darling" that should have been murdered!). "Words are intoxicating . . it is permissible for a writer to get on an occasional jag with fine phrases, but he must not make a drunken nuisance of himself in public."[4]

10. Nonumque prematur in annum is Horace's age-old advice to the budding poet; and although it would be fatal to a modern medical paper to store it away for quite this long, the principle is important. The manuscript should always be put out of mind and lie fallow for a time—a couple of weeks or a month or two—and then be brought back into the light for a final polish.

11. Shorten Everything: Finally, we should once again make sure that everything is as short as it should be—words, sentences, paragraphs, the opus itself. It is useful to "flesch" our writing. Rudolph Flesch[5] has given us a number of arbitrary yardsticks for measuring readability. Two of these are easily applied and are particularly applicable to medical writing: length of sentences and number of affixes per hundred words are counted and then the standard of readability is read off from Table 1. A little later we will flesch a piece of prime pudder.

TABLE 1
"Flesching" Values

Average Sentence Length (No. of Words)	Readability	Affixes per 100 Words (No.)
8 or less	Very easy	22 or less
11	Easy	26
14	Fairly Easy	31
17	Standard	37
21	Fairly Difficult	42
25	Difficult	46
29 or more	Very Difficult	54 or more

THINGS TO AVOID

So much for things to do; now for the pitfalls to avoid.

1. Verbal Bums, Pudder and Gobbledygook: All examples are taken from articles in print or from manuscripts seriously submitted by serious-minded authors to serious journals; they are culled, in fact, without any very diligent search from the finished writings of our colleagues.

"Verbal bums," according to Robert Gill, are "idle words that are doing no one any good."[6] He estimates that at least 15 per cent of the words in print today are idle, and he points out what this means in terms of time wasted, money spent, library space taken up and so on. If these dead branches alone were cut off, the blessing would be great. Here are a few examples:

> "Insofar as potassium is concerned it can be stated with a fair degree of assurance that deficits of this ion can occur in congestive failure."

The twenty words from "insofar" to "ion" mean exactly this:

> "It is fairly certain that potassium deficits"

Seven words instead of twenty; thirteen words, or 65 per cent of the original twenty, are bums.

> "As regards clinical manifestations, there are three types of clinical dysentery."

The first four words are clearly idle and add nothing to the last six. Incidentally, the author means "clinical types" rather than "clinical dysentery." Sloppy thinking and sloppy writing. Again,

> "The patient suffered with pains in her lower extremities at night, in connection with which her doctor gave her Seconal to help her to sleep."

"In connection with which" are the plainest bums in this multitude. But "had" is as good as "suffered with"; "legs" (or "calves" or "thighs") is infinitely preferable to "lower extremities"—one wonders that this pudderer missed the opportunity to say "inferior extremities"; and the "to" before sleep can be dispensed with, for some infinitives are quite happy to stand alone. On further reflection is it really necessary to tell medical readers that Seconal was given to encourage sleep? The stripped sentence now nakedly reads:

> "The patient had pains in her legs at night for which her doctor gave her Seconal."

Questionable medicine, perhaps, but plain and simple English at last.

Another sample, written by a distinguished dean of medicine:

> "Evidences of DGG may progress slowly in seriatim fashion."

If the Latin adverb must be used, it is as sturdy as any other and can stand on its own feet; it does not need to be supported between two meaningless English bums. If "in" and "fashion" are to be used, fashion, being a noun, must be qualified by an adjective, presumably "serial." But "one by one," in place of the whole original phrase, is both simpler and better English.

A special form of verbal bumming is tautology; the writer, when he wants to say simple things like lecture, tumor, neurogenic, disease, firm or red, ties his parcel up in a redundant knot and delivers it as didactic lecture, tumor mass, of neurogenic origin, disease entity, firm in consistency, or red in color.

So much for verbal bums. For our purposes pudder and gobbledygook need not be sharply differentiated. King Lear's "pudder" has been reincarnated by Ivor Brown to mean "jargon of the learned or of those pretending to rare wisdom," and gobbledygook was applied by Maury Maverick to the sort of writing that reminded him of the "ludicrous pomposity" of the strutting turkey gobbler. Examples are not hard to find among the writings of our "literary" colleagues:

"The methodology utilized . . .," when translated into good English reads "the method used . . . ."

"A substantial moiety of the totality of cases . . ." presumably means "most of the cases."

"Hematologic difficulty" must surely mean an unsuckable bone marrow or some such obstacle to the practice of hematology. Pudderers, however, use it to mean "blood disease."

"Further anamnestic elements were unremarkable." Imagine going to these pains to paraphrase "the rest of the history . . . ."

"A cachectic female with poor hemic component." This poor wretch when unpuddered is presumably "a cachectic woman with anemia."

"Macular areas non-pruritic in nature." "In" and "nature" are a couple of bums because they add nothing to "non-pruritic macular areas." But how about "patches (or macules) that don't itch?"

And finally for a supreme piece of psychiatrese:

> "For instance, to treat patients by means of hormones, as insulin or adrenal cortical extract, or by means of carbon dioxide, is to attempt to improve the personality aberrations by altering the disturbed neuro-humoral integrative processes in the hierarchy at the relatively low degree of integrative complexity involving complex molecular configurations, and thus secondarily influence the more complex integrative processes, and cause a healthier integration of the most complex integrative processes of personality."

"Flesched," this sentence of seventy-three words bristles with fifty-two affixes, i.e., seventy-one per hundred words. A glance at the flesching table (Table 1) confirms that this execrable prose is quite beyond the pale.

2. Footnotes should always be used, like parentheses, as though you had a ration of one for the rest of your life. Some material is appropriate to a footnote but, in general, matter important enough to set up in type is important enough to include in the text. A footnote to the reader is said to be like a fire alarm to the honeymooner—it does something awful to the train of thought.

3. Repetitious legends that echo the text are infuriating. Brief repetition is often inevitable but it should be kept to a minimum; and material that is appropriate to the legend should, as a rule, be excluded from the text. The same caution applies to rehashing material that is clearly set out in a table.

4. *Former and latter should never be used.* They invariably send the reader back on an identity-hunt. Repeat the word or phrase and never be afraid to do this in the interest of clarity. A similar guiding light should protect us from

5. Elegant Variation: I referred earlier to manuscripts "*seriously* submitted by *serious*-minded authors to *serious* journals." The elegant variationist, because he entertains the superstition that the same word should not be repeated, would have labored to produce something like: "earnestly submitted by serious authors to reputable journals" and the sentence would have lost what force it has. As Fowler[7] says, "it is those intent rather on expressing themselves prettily than on conveying their meaning clearly, and still more those whose notions of style are based on a few misleading

rules of thumb, that are chiefly open to the allurements of elegant variation . . . There are few literary faults so widely prevalent." The misunderstood rule is that it is better to avoid repeating the same word *in a different sense;* for example, it is better not to write "they passed their time passing catheters."

6. Jingles and false scents are minor blemishes, but they can be irritating to the weary reader because they distract his attention and he then ceases to be affected precisely as you wish. Jingles are repetitions of similar sounds as in "the actual value of factual knowledge" or "Jinglestein has amassed a mass of statistics." False scents can be even more distracting: "The choice so far as we can tell lies between . . ." The sequence "tell lies" catches the reader's eye and starts an unintended train of thought.

Finally, there are two prejudices that require consideration: these concern the "perpendicular pronoun" and the split infinitive. Both of these are permissible and often desirable, but they are shrouded in so much prejudice that they are usually better avoided.

The perpendicular pronoun, "I," unfortunately tends to erect a personal barrier between writer and reader; it is therefore better avoided whenever possible and this is usually easy enough with a little rearrangement. But at times it cannot be avoided without ambiguity or clumsy circumlocution, and it is then better to say "I." Above all, do not refer to yourself fondly as "the author" or regally as "we." According to Mark Twain the only people who have the right to use the royal "we" are presidents, editors and people with tapeworms.

To Split or Not to Split

Infinitives split just as naturally as peas and personalities, yet the virginity of the infinitive is so jealously guarded by her champions that splitting has become a literary hazard. In his own ignorance the split-infinitive snooper regards the splitter as an ignoramus—and that is not to affect the reader precisely as one wishes. The truth is that a judiciously split infinitive is a desirable device when it is used to avoid ambiguity or artificiality. "Every good literary craftsman," says Bernard Shaw, "splits his infinitives when the sense demands it." Anyone who takes this stand has the unanimous backing of the highest authorities—Jespersen, Fowler, Quiller-Couch, Gowers.[8]

G. K. Chesterton, master of words, instinctively writes:

> "We understand, however, that we are *to well and truly try* the case between our sovereign lord the King and the prisoner at the bar, neither of whom has put in an appearance as yet."

This is a resounding cleavage if ever there was one, yet what could be better or more natural? Put "well and truly" elsewhere in the sentence and the writing immediately becomes amateurish and awkward. "Well and truly" *has* to appear immediately in front of "try" to give the phrase its full and intended force.

And there are other adverbial phrases that must brush the "to" aside and lean against the verb. Consider "he had enough courage *to more than compensate* for his frail physique." It is quite impossible to put "more than" anywhere else and be left with exactly the same meaning; "more-than-compensate" is a complete and indivisible predicate.

Taste and discretion should be one's guide. for splitting can be both good and bad. Fowler[7] divides the English-speaking world into the following five classes:

> (1) those who neither know nor care what a split infinitive is
> (2) those who do not know, but care very much
> (3) those who know and condemn
> (4) those who know and approve
> (5) those who know and distinguish

It is to the last enlightened class that we should all strive to belong, although of course class 1 is the really happy breed with no cares at all. The second class is a melancholy group who waste their time avoiding good constructions, such as "to be really raped," and write "really to be raped" instead, believing that by so doing they are preserving the virginity of the infinitive if not their own. Members of the fourth class are to be admired for their valor but not necessarily for their discretion. It is the third class, however, that gives most trouble to the discriminating fifth class, for it contains the whole lusty band of ignorant snoopers who pounce with glee upon each and every split infinitive.

In conclusion let the forthright Bernard Shaw sound a valedictory warning to all snoopers. Many years ago he wrote to the editor of the London Times:

> "There is a busybody on your staff who devotes a lot of his time to chasing split infinitives I

call for the immediate dismissal of this pedant. It is of no consequence whether he decides to go quickly or to quickly go or quickly to go. The important thing is that he should go at once."

Kernahan has said that "There are two literary maladies—writer's cramp and swelled head. The worst of writer's cramp is that it is never cured; the worst of swelled head is that it never kills." I would add a third malady—writer's itch. Now in contrast to the other two, the itch to write is an infection worth catching; for writing, properly undertaken, "maketh the exact man" which every man of science must surely strive to be. Writer's itch becomes deplorable only when it is pudderized into an "auctorial pruritus."

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Clinical Studies

Selective Angiocardiography in the Diagnosis of Atrial Septal Defect (Ostium Secundum Type)*

EDUARDO COELHO, M.D., EDUARDO DE PAIVA, M.D. and AMERICO NUNES, M.D.

Lisbon, Portugal

ANGIOCARDIOGRAPHY is very important for the anatomic and physiologic diagnosis of interatrial septal defect and supplies much important data.[1-16] It not only demonstrates the anatomic septal defect but also delineates its upper and lower limits. Since the pathophysiologic alterations are proportional to the volume of blood shunted and this is correlated with the size of the septal defect, angiocardiograms indicate the severity of the pathophysiologic alterations.

We always use selective angiocardiography. With this technic the catheter is allowed to progress from the right into the left auricle where the 76 per cent solution of Urographin is injected. If the left auricle cannot be reached, the contrast medium is injected into the right ventricle; and in the second phase of the angiocardiogram (levocardiogram) the opacification of the right atrium immediately follows that of the left atrium; sometimes the contrast medium is injected into the left ventricle.

In some cases selective angiocardiography provides the differential diagnosis between *ostium secundum* and *ostium primum*. An almost simultaneous opacification of all chambers strongly favors the diagnosis of *ostium primum*. However, a very large defect in cases of *ostium secundum* may produce the same picture. In one patient whose diagnosis was confirmed by surgery, the catheter left the left auricle where it had been placed and re-entered the right auricle where the injection was made. Opacification of the right auricular appendage and of the right auricle was first observed, followed by visualization of the right ventricle, pulmonary artery and left auricle as the contrast radiopaque medium passed through the septal defect because of the injection pressure. The levoangiocardiogram demonstrated that this passage was due to an interatrial septal defect and not to a patent foramen ovale, because after the injection all chambers were opacified, the pulmonary artery being clearly visualized at the same time. There was opacification of all cardiac chambers and great vessels during the levocardiogram as in cases of *ostium primum*.

Double transseptal catheterization (the catheters being simultaneously introduced through the saphenous vein and through an antecubital vein) adds further valuable information and supplements the results obtained from selective angiocardiography.

CLINICAL EXPERIENCE

Experience with twenty cases of atrial septal defect (ostium secundum type), either simple or associated with anomalous drainage of the pulmonary veins, is described in this report. They included twelve female and eight male patients whose ages ranged between five and forty-six years.

In six cases one or two pulmonary veins entered the right atrium and in one, the superior vena cava. This anomaly was demonstrated by the introduction of the catheter through the respective veins under fluoroscopic

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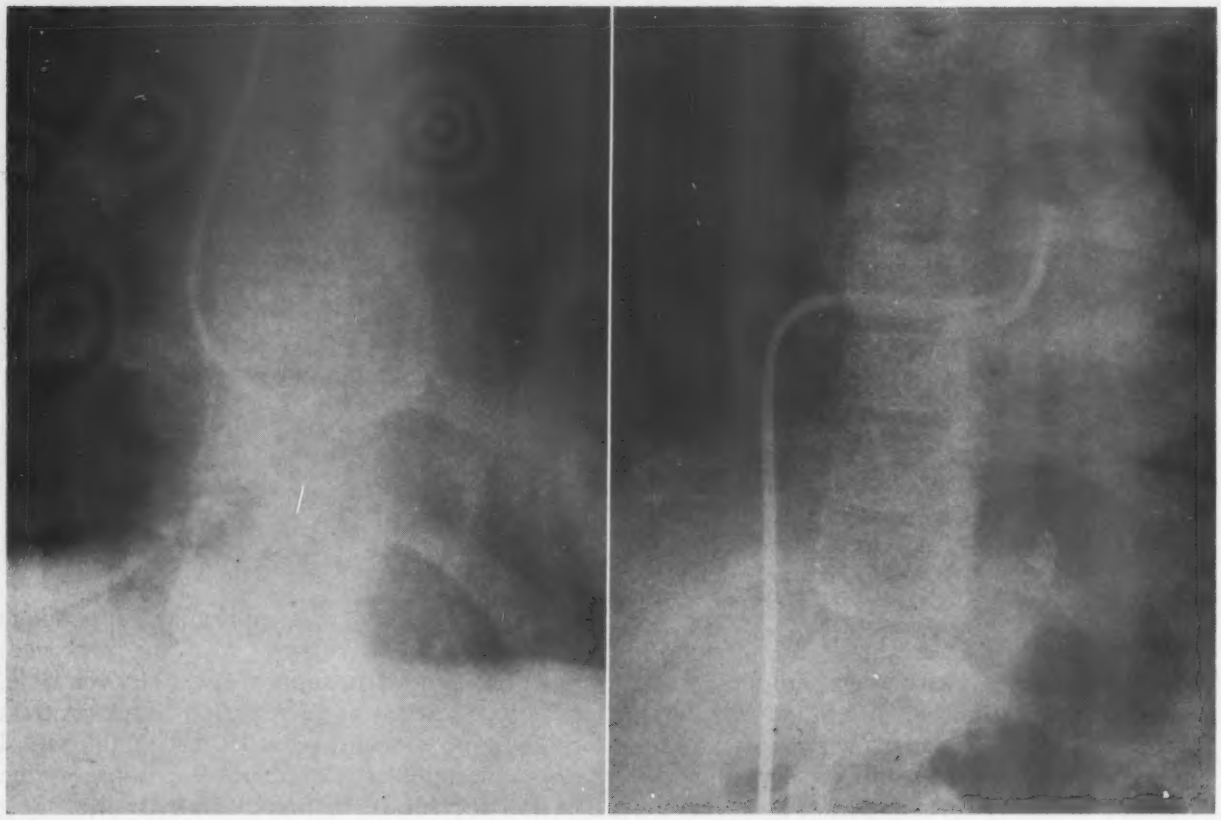


A B

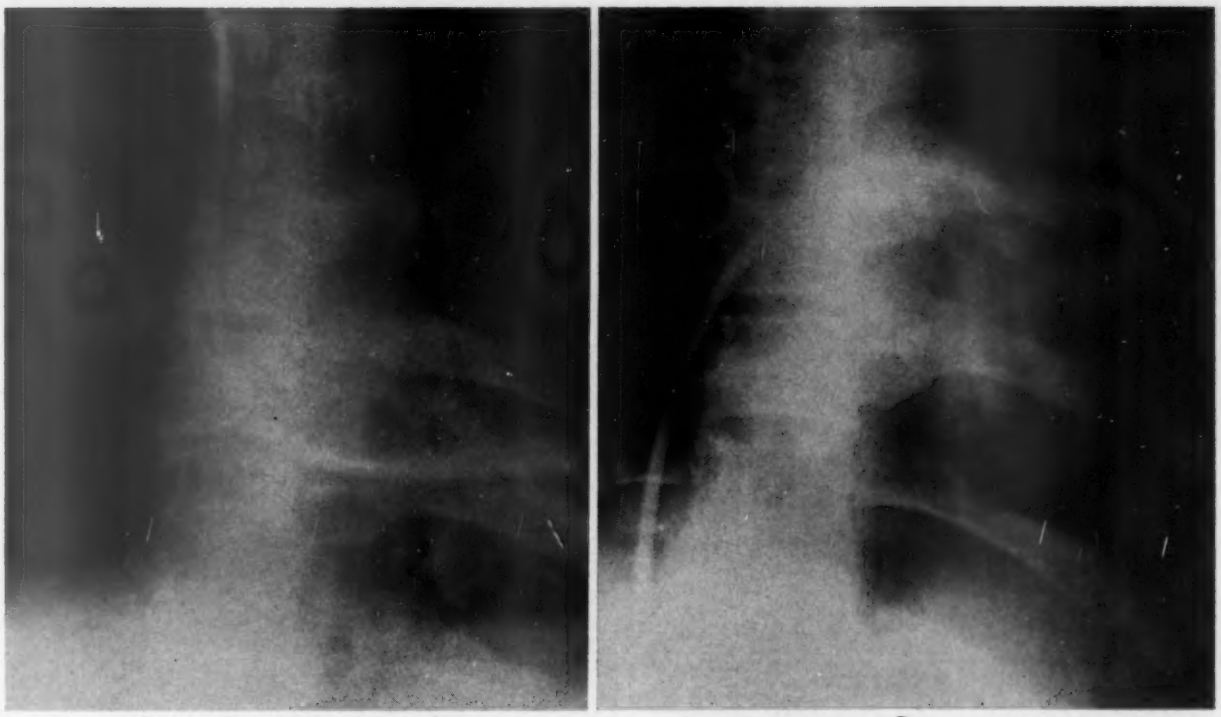
FIG. 1. A and B, ostium primum, left auricle (tip of catheter).

control during catheterization or, as in one case, during angiocardiography. Drainage of a pulmonary vein into the right auricle alone may simulate the functional conditions of atrial septal defect with left to right shunt and in these cases an increase in the oxygen concentration in the right auricle of 2 volumes per cent or more is not enough to demonstrate the existence of an atrial septal defect.[17-19]

FIG. 2. Ostium secundum, left auricle (tip of catheter).

Catheterization Findings: The oxygen concentration in the right auricle was not increased in eight cases. In two patients the oxygen concentration in the right ventricle was increased above the auricular level. Besides the left to right shunt, some patients demonstrated a small right to left shunt due to asynchronism of the auricular contractions, the end of the right auricular systole coinciding with the beginning of the left auricular diastole. Varying in proportion with the volume of blood shunted, pulmonary blood flow in some cases was three times the systemic flow. The oxygen saturation of the peripheral blood was between 90 and 96 per cent. A decrease of peripheral oxygen saturation producing cyanosis was observed in some cases, as Dexter[20] has also demonstrated.

In large defects the pressure gradients between the two atria were small or absent; in small defects marked differences of 3 to 4 mm.



A B

FIG. 3. A and B, ostium secundum, left ventricle (tip of catheter).

Hg in the mean pressure were found. Since the catheter may enter the left auricle in cases of patent foramen ovale without a septal defect, this fact does not warrant the diagnosis of interatrial septal defect and one must be careful to distinguish between these two conditions.

Right ventricular systolic pressures reached values of 40 to 50 mm. Hg in fourteen cases. In one case of Lutembacher syndrome the systolic pressure was 91 mm. Hg. The pulmonary "capillary" pressure varied between 8 and 15 mm. Hg. Besides allowing us to determine the increase in the oxygen concentration in the

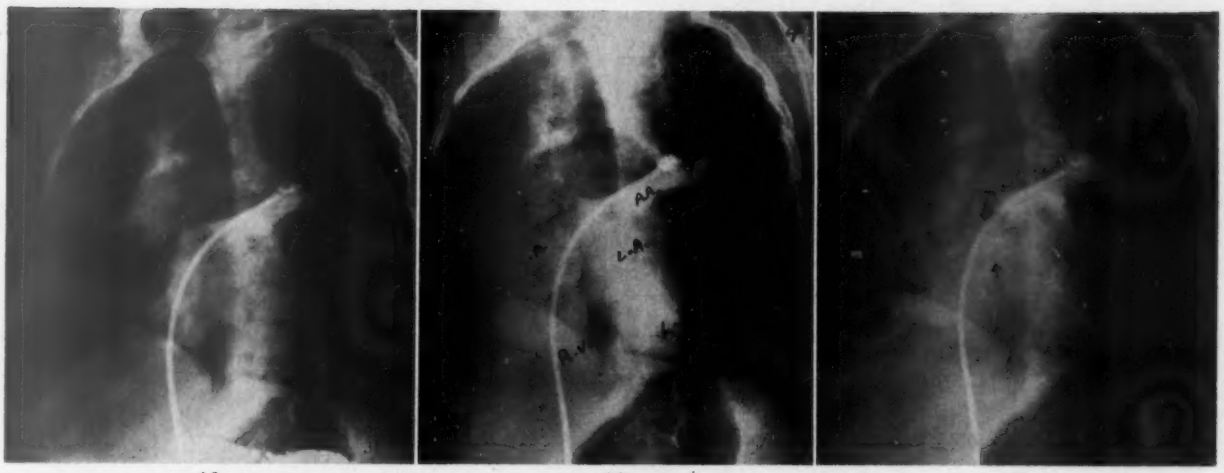
FIG. 4. Ostium secundum, left ventricle (tip of catheter).

FIG. 5. Foramen ovale.

Fig. 6. Case 1. The branches of the pulmonary veins and the auricular appendage are outlined.
Fig. 7. Case 1. The contrast medium passing from the left auricle to the right auricle.
Fig. 8. Case 1. The opacification of the four heart cavities in systole.
Fig. 9. Case 1. The opacification of the four cavities in diastole.

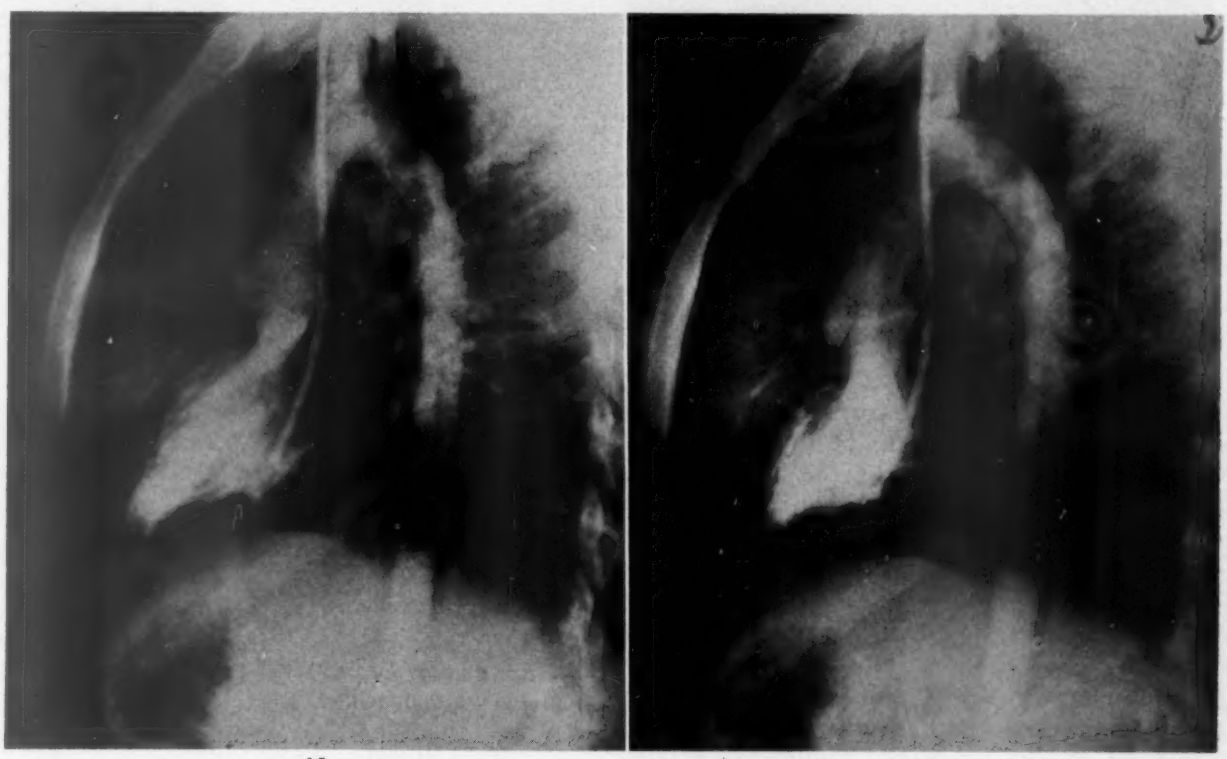
right auricle, the pressures in the different chambers, the volume of the left to right shunt and the increase in the pulmonary blood flow, the catheter through its different positions may permit the differential diagnosis in cases of ostium secundum and ostium primum and may even indicate the approximate dimensions of the defect.

Differentiation of Ostium Secundum and Ostium Primum Defects: The Mayo Clinic group[21] has shown that in cases of ostium secundum the catheter, after passing the septal defect at the center of the cardiac silhouette, progresses in a stepwise fashion toward the left ventricle; on the other hand, in cases of ostium primum defect it progresses down toward the lower border of the cardiac shadow and thence moves up toward the left atrium.



10 11 12

FIG. 10. Case 2. The contrast medium passing from the left auricle to the right auricle.
FIG. 11. Case 2. The contrast medium in the four cavities; interventricular septum.
FIG. 12. Case 2. The dimensions of the atrial septal defect correspond to the space between two arrows.



13 14

FIG. 13. Case 3. The aortic cusps in diastole.
FIG. 14. Case 3. The aortic cusps open (systole).

Besides these peculiarities of position in either type of interatrial septal defect, we have observed the following features: *Ostium primum:* When the catheter is introduced via the saphenous vein, it reaches the right auricle, progresses toward the left auricle forming an angle of 90° and then is directed upward (Fig. 1B). When introduced through an antecubital vein, the catheter follows, as a rule, the direction described by the Mayo Clinic investigators (Fig. 1A). *Ostium secundum:* When the catheter is introduced through the saphenous vein, it reaches the right auricle and enters the left auricle through the septal defect, forming a curve concave to the left (Fig. 2). On other occasions it forms an arch, being deflected downward toward the left ventricle (Fig. 3B).

When the catheter is inserted through an

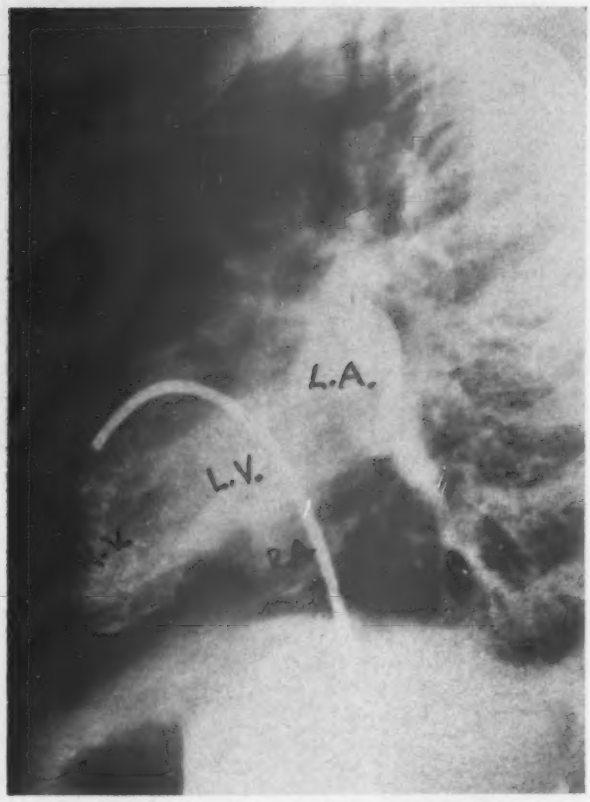


FIG. 15. Case 4. The tip of the catheter in the right ventricle during levoangiocardiogram.

antecubital vein, it either enters the left auricle at once or progresses rapidly toward the left ventricle through the left auricle, without permitting a recording in this chamber (Figs. 3A and 4). In the former instance it describes a small curve, in the latter a great arch. Sometimes it is possible to evaluate the size of the septal defect by catheterization. If one catheter is introduced through the saphenous vein and a second one is inserted via one of the antecubital veins, the first marks out the upper position of the defect and the second enters near its lowest portion. Surgery has confirmed this fact once in our series. Figure 5 shows two catheters introduced via the saphenous and antecubital veins, respectively, crossing simultaneously through the patent foramen ovale.

Illustrative Angiocardiograms

The angiocardiograms of the followings seven cases illustrate different problems encountered by us.

Case 1. The catheter was introduced via the saphenous vein, passed through the right auricle to the left auricle and the tip lodged in a pulmonary vein. Figure 6 shows some clearly outlined branches of the pulmonary veins and the auricular appendage. In Figure 7 the contrast medium passes through the atrial septal defect to the right auricle. In Figures 8 and 9 we see the opacification of the four heart cavities in systole and in diastole. The interventricular septum is clearly shown. The aorta is of a reduced caliber, a characteristic of cardiopathies with reduced systemic circulation.

Case 2. The tip of the catheter is placed in the left auricular appendage. The contrast medium passes from the left auricle to the right auricle which appears partially opacified (Fig. 10). In Figure 11 the contrast medium is in the four cavities and the interventricular septum is clearly seen. The approximate dimensions of the atrial septal defect correspond to the space between the two arrows in Figure 12. This amounts to 2.5 cm. if the distortion from the nearness of the cathode ray tube is considered.

Case 3. The catheter introduced via the antecubital vein passed from the right auricle to the left auricle and thence to the left ventricle (Fig. 13). The initial images show only the left ventricle, the aorta and the coronary arteries opacified. Figure 13 shows the aortic cusps in diastole, and Figure 14 the ventricle in systole with open cusps. Since the contrast medium injected into the left ventricle appeared only in this chamber, the aorta and the coronary arteries throughout the angiocardiographic examination, the existence of a common atrioventricular canal or of a ventricular septal defect is excluded. At operation a large atrial septal defect was found in this patient.

Case 4. We could not insert the catheter in the left auricle and therefore directed the tip to the right ventricle. During the levoangiocardiogram we demonstrated the existence of an atrial septal defect. Figure 15, during levogram, shows the tip of the catheter which has been introduced via the saphenous vein lodged in the right ventricle. The contrast medium was injected here and we see the four cavities, the right auricle and ventricle reopacified by a left to right shunt at the auricular level since the right auricle is also opacified.

Case 5. In Figure 16 the catheter was introduced via the saphenous vein and directed to the left auricular appendage into which the injection was made. The contrast medium passes to the right auricle through a septal defect and opacifies the inferior vena cava at the same time. Figure 17 shows the opacification of the four cavities. We clearly see the space corresponding to the interventricular septum. The simultaneous opacification of the right auricle and the inferior vena cava shows this is a case of auricular septal defect of the inferior vena cava type.

Case 6. Sometimes the catheter may easily enter the left auricle in cases of patent foramen ovale

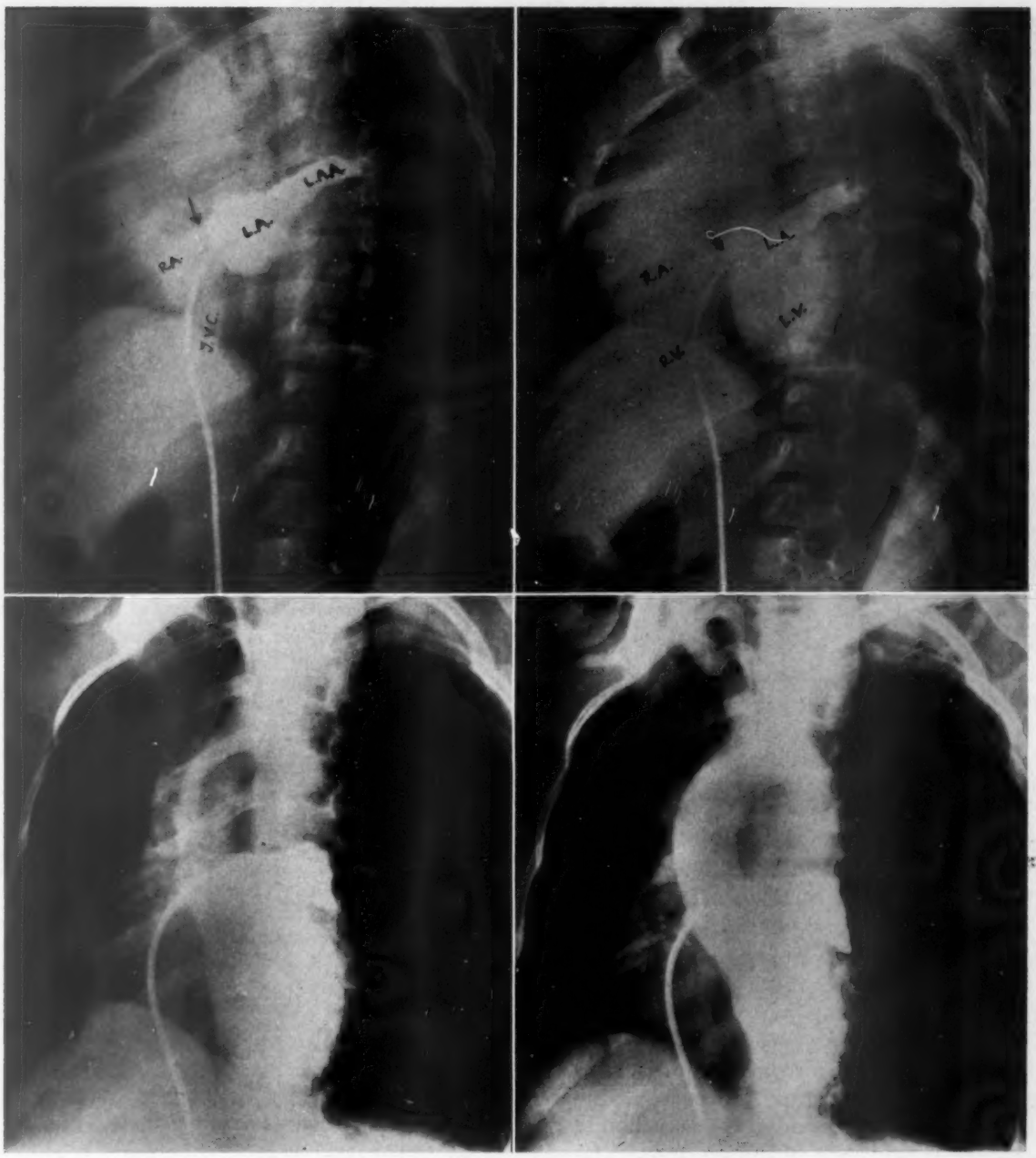


Fig. 16. Case 5. The catheter in the left auricular appendage.
Fig. 17. Case 5. The opacification of the four cavities; the interventricular septum.
Fig. 18. Case 6. Slight opacification of the aorta provoked by the previous systole.
Fig. 19. Case 6. Opacification of the aorta and its branches; the auricle in diastole, the ventricle in systole.

without atrial septal defect as shown in Figure 18. Immediately above the upper limit of the left auricle we see a slight opacification of the aorta provoked by the previous systole; the outlines of the interauricular and interventricular septum are very distinct, the contrast medium not passing to the right cavities. When the auricle is in diastole and the ventricle in systole, we see clear opacification of the aorta and its branches (Fig. 19).

Case 7. A small defect of the septum of patent foramen ovale type can permit the contrast medium to pass into the right auricle but in such a small quantity that the outline of the right cavities is not clear. This occurred in Figure 20 in which the catheter via the saphenous vein was lodged in the left auricular appendage.

Summary

The authors studied twenty cases of atrial septal defect (ostium secundum type), simple

FIG. 20. Case 7. The tip of the catheter is placed in the left auricular appendage.

or associated with anomalous drainage of the pulmonary veins. The position of the catheter at the level of the septum when it is introduced via the saphenous or antecubital veins may permit the differential diagnosis between ostium primum and ostium secundum.

The angiocardiographic characteristics of atrial septal defect, when the contrast medium is injected into a pulmonary vein, left auricle, left ventricle or right ventricle, are described. Angiocardiography makes it possible to establish the size of the atrial septal defect. The results of angiocardiography are more valuable if supplemented by a study of the position of two catheters introduced simultaneously via the saphenous and antecubital veins.

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Intracardiac Myxomas and Thrombi

Clinical Manifestations, Pathology and Treatment*

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CARDIAC TUMORS are relatively infrequent lesions which have assumed clinical importance as successful methods for intracardiac surgery have been developed. Recent reports indicate the increasing frequency of accurate preoperative diagnosis and the successful removal of such tumors.[1–36]

The first recorded primary cardiac tumor, described by Columbus[37] in 1559, arose within the left ventricular cavity. Since that time approximately 550 primary tumors of the heart have been reported. Over 300 have been myxomas. This tumor typically arises from the atrial septum in the region of the fossa ovalis. It is three times more frequent in the left atrium than in the right.[1,38] In twenty-one instances the diagnosis has been made antemortem and in thirty cases myxomas have been discovered during surgical exploration for mitral or tricuspid stenosis.

Intracardiac tumors may occur at any age. The majority have developed in patients between the ages of thirty and sixty years. The incidence has been greater in women. The usual clinical manifestations arise from obstruction of the mitral or tricuspid valve. In recent years angiocardiography has resolved many of the difficulties inherent in establishing an accurate preoperative diagnosis.[39–41] Until the advent of technics for stasis cardiotomy and temporary cardiopulmonary bypass which permit the excision of such tumors under direct vision, attempts at removal of intracardiac tumors were crude and inexact.[42]

Because an accurate preoperative diagnosis of a primary cardiac tumor or thrombus can be made if certain clinical and roentgenographic characteristics are kept in mind, our experience with the following three cases is presented to elucidate the diagnostic features and characteristics of such lesions. In the first patient (Case 1), a right ventricular myxoma was suspected on clinical examination and confirmed by angiocardiography. This tumor arose within the right atrium and had prolapsed through the tricuspid valve into the right ventricular cavity. In the second case a large left atrial thrombus, not suspected prior to death, was revealed on postmortem examination in an elderly woman with emboli in the pulmonary and mesenteric arteries and subsequent extensive infarction. In the third case, postmortem examination revealed a large mural thrombus completely filling the distal two-thirds of the left ventricular cavity with multiple mural thrombi within the cardiac chambers. Chronic myocarditis was responsible for the thrombi and death resulted from low cardiac output and multiple pulmonary and systemic emboli. Peripheral emboli and a low cardiac output were responsible for gangrene of the right foot, right fourth finger and third left toe.

CASE REPORTS

CASE 1. A thirty-three year old white salesman was admitted to Vanderbilt University Hospital on October 2, 1959, for evaluation of progressive dyspnea, fatigue and dizziness of approximately fifteen months' duration. He had been hospitalized elsewhere eight months previously with similar symptoms but, in addition, complained of precordial pain, loss of weight, "fainting" and "painful" throbbing neck veins. At that time, the blood pressure was 110/80 mm. Hg and an apical systolic murmur and pericardial friction rub were audible. Laboratory examinations failed to disclose any striking abnormality. The venous pressure was 100 mm. of saline and the arm-to-tongue circulation time

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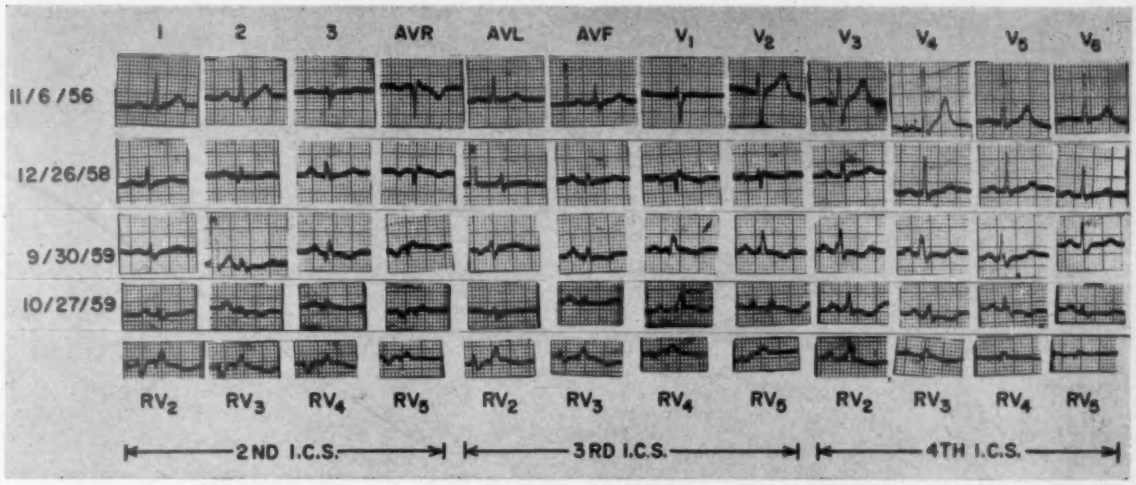


FIG. 1. Case 1. Serial electrocardiograms of patient with right ventricular tumor originating within the right atrium.

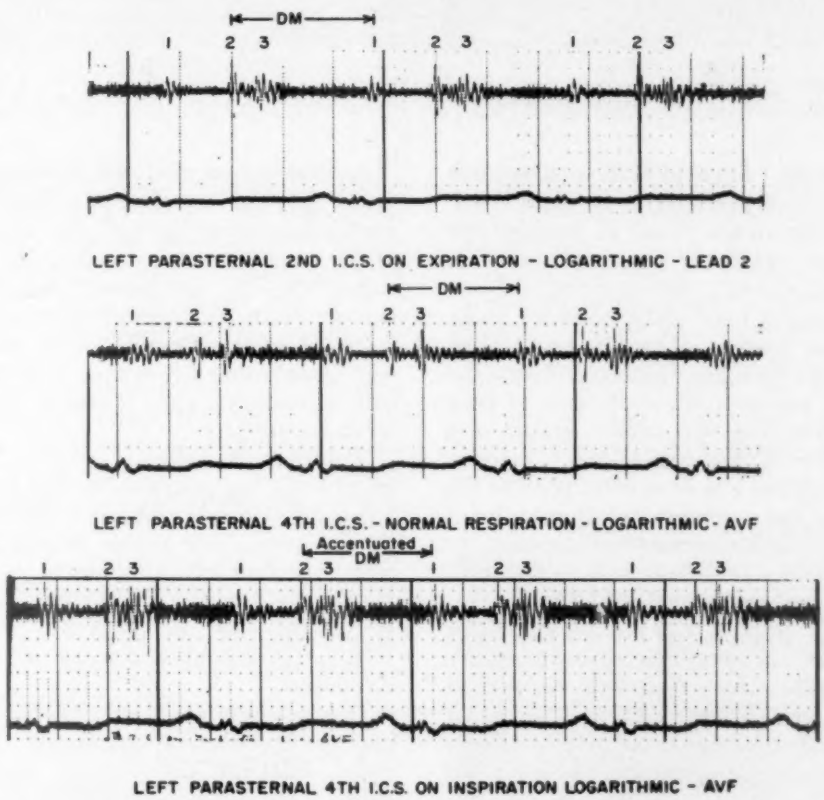
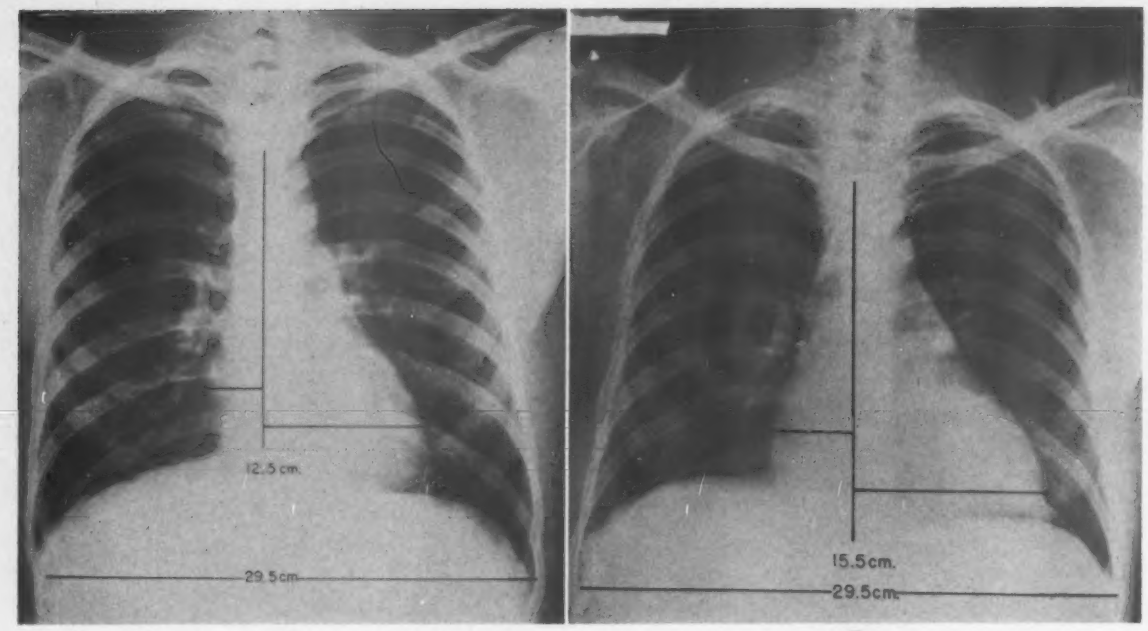

DM
1 2 3
LEFT PARASTERNAL 2ND I.C.S. ON EXPIRATION - LOGARITHMIC - LEAD 2
LEFT PARASTERNAL 4TH I.C.S. - NORMAL RESPIRATION - LOGARITHMIC - AVF
Accentuated
LEFT PARASTERNAL 4TH I.C.S. ON INSPIRATION LOGARITHMIC - AVF

FIG. 2. Case 1. Phonocardiograms demonstrating high frequency holodiastolic murmur with third sound 0.11 to 0.13 second after accentuated second sound.

was twenty-two seconds. A roentgenogram of the chest revealed no abnormalities. The electrocardiogram was considered compatible with acute pericarditis. No definite etiologic agent was discovered and the patient was discharged with a diagnosis of acute nonspecific pericarditis. During the ensuing eight months symptoms increased and he experienced "cramps" in both legs on exertion and reclining.

Past history indicated that three years prior to hospitalization the blood pressure had been 122/84, no cardiac murmurs were audible and the electrocardiogram was within normal limits (Fig. 1).

On physical examination, the patient was able to lie comfortably in bed without dyspnea or orthopnea. The blood pressure was 100/76 mm. Hg and generalized cyanosis was present. The cervical veins were strikingly distended and displayed a prominent A wave. Multiple, superficial dilated veins were



A B

FIG. 3. Case 1. Roentgenograms of chest. A, February 26, 1954; B, October 3, 1959.

present on both thighs. Physical findings suggestive of pleural effusion were noted over the right lower thorax. No right ventricular heave or palpable left ventricular impulse could be demonstrated. A grade 2 blowing holodiastolic murmur and a prominent third heart sound were clearly audible along the left parasternal border. The murmur varied with respiration and with change in the position of the patient. The first and second sounds were of poor quality (Fig. 2). The liver was tender, smooth and enlarged 7 cm. below the right costal margin. Minimal shifting dullness was demonstrated over the abdomen but there was no peripheral edema. Painful internal and external hemorrhoids were present.

Laboratory examination revealed a hemoglobin of 15.7 gm. per cent and a hematocrit of 50 per cent. The urine specific gravity was 1.022 and large amounts of protein and urobilinogen were present. Liver function studies showed marked impairment of function. The venous pressure was 320 mm. of saline and the arm-to-tongue circulation time was forty-eight seconds. A spirogram was within normal limits.

The electrocardiogram revealed right bundle branch block with an initial Q wave in V_1, low voltage and large P waves (Fig. 1).

Cardiac fluoroscopy and roentgenograms demonstrated fluid at the base of the right lung. The cardiac pulsations were full and right atrial and ventricular enlargement was noted. An area of infiltration compatible with pulmonary infarction was seen in the lower lobe of the right lung. A review of serial roentgenograms taken between 1954 and 1959 showed a progressive increase of 3 cm. in the cardiac transverse diameter (Fig. 3).

Angiocardiograms disclosed a persistent, large filling defect almost completely obliterating the right ventricular cavity in both the frontal and lateral films, suggesting the presence of an intracardiac tumor (Fig. 4). The tumor appeared to be approximately 8 cm. in diameter and originated near the tricuspid valve. Because of the smooth contour, it was thought that this shadow represented a myxoma arising within the right atrium or in the region of the tricuspid valve.

Treatment and Surgical Findings: The patient was given a 500 mg. sodium diet and 100 mg. of hydrochlorothiazide was administered daily. Within ten days a twenty-five pound diuresis occurred. The blood pressure fell progressively to 90/75 mm. Hg, the venous pressure to 280 mm. of water and the circulation time to thirty-two seconds. Icterus, transient personality and occasional psychotic changes developed.

Operation was performed October 30, 1959 under general endotracheal anesthesia. A standard anterior bilateral thoracotomy incision was made through the fourth interspaces with transection of the sternum. The lungs were essentially normal except for atelectasis of the lower lobe of the right lung. After opening the pericardium, a round, globular mass was apparent in the right ventricle during systole. During intracardiac palpation through the right atrial appendage, the tumor was dislodged from the right ventricle into the right atrium. Temporary cardiopulmonary bypass was instituted with a pump oxygenator. The right atrium was opened widely and a myxoma 8 cm. in diameter was delivered from the right atrial cavity (Fig. 5). The myxoma was attached by a pedicle to the posterior

A B

FIG. 4. Case 1. The posterior-anterior (A) and right lateral (B) angiocardiograms demonstrate a 6 second delay of the contrast media within the right atrium; a large filling defect within the right ventricular cavity. The tumor originates within the right atrium and measures 8 cm. in diameter.

wall of the atrium between the orifices of the inferior vena cava and the coronary sinus. The pedicle was cut flush with the posterior atrial wall. The tricuspid valve leaflets were inspected and appeared normal. The atriotomy was closed and cardiopulmonary bypass discontinued after a total time of ten minutes.

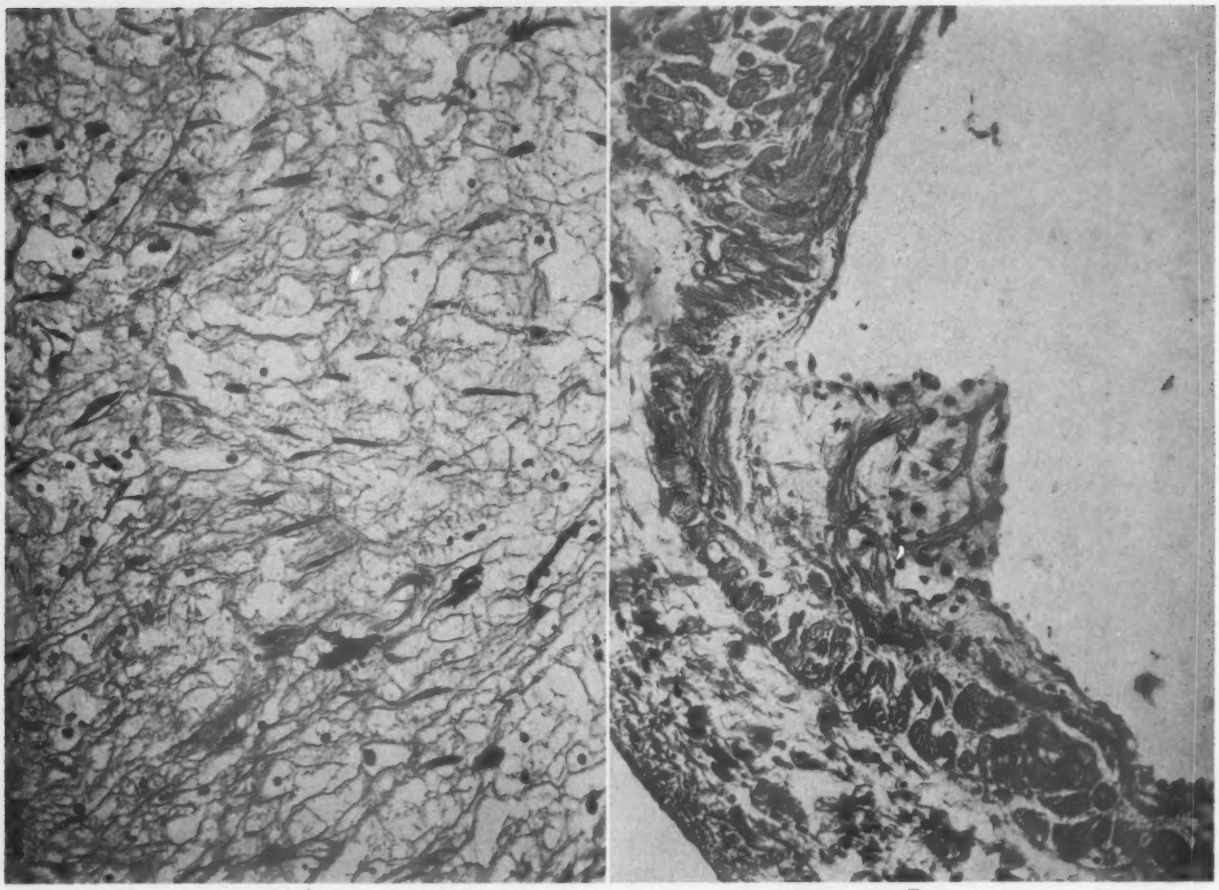
Preoperatively, the right atrial pressures were 23/13 mm. Hg, with a mean pressure of 15 mm. Hg; the right ventricular pressures were 15/5 with a mean of 10; the pulmonary arterial pressures were 16/8 with a mean of 12 and the brachial arterial pressures were 75/60. Postoperatively, the right atrial pressures were 22/11 with a mean of 16 mm. Hg; the right ventricular pressures were 23/6 with a mean of 16; the pulmonary arterial pressures were 23/13 with a mean of 15 and the brachial arterial pressure was 140/90 mm. Hg. The venous pressure decreased from 23 to 10 mm. Hg.

Pathologic Findings: The tumor was an 8 by 6 by 4.5 cm. oval mass. The surface appeared generally translucent, smooth and glistening, with a thin capsule. It was bluish gray with yellow hemorrhagic portions. On transection, the tumor was composed of an outer capsule of variable thickness and a center of gelatinous consistency. A few areas were reddish-brown and resembled infarction and necrosis; other areas appeared fibrotic.

Microscopically, the tumor was covered with endocardium and composed of loose myxomatous connective tissue (Fig. 6A). Strands of dense fibrous connective tissue and stellate cells were present throughout the stroma. The tumor was vascular with irregularly shaped endothelial channels. Many bright eosinophilic areas suggested a fibrin net enclosing degenerated blood cells. At the periphery, capillaries and fibroblasts were actively growing into this area.

Postoperative Course: Postoperatively the electrocardiogram demonstrated a nodal rhythm at a rate of 88 per minute. There was an initial improvement in voltage and the previous qR pattern of right bundle branch block in leads to the right of the precordium had disappeared; the more classic variety of right bundle branch block with an AR′ pattern appeared.

FIG. 5. Case 1. The oval myxoma (8 by 6 by 4.5 cm.) is superimposed over the filling defect within the right ventricular cavity.



A B

FIG. 6. Case 1. A, microscopic section of tumor reveals loose myxomatous tissue with a few stellate cells throughout the stroma. (Orginial magnification approximately × 200.) B, microscopic section of the right atrial appendage reveals another nodule of loose myxomatous tissue on the endocardium resembling the excised tumor. (Original magnification approximately × 100.)

For thirty-six hours, the patient's postoperative course was uneventful with the exception of a moderate amount of bloody drainage from the right thoracic cavity. Following this, however, acute biventricular failure developed and the patient died within twelve hours despite therapy.

Postmortem examination revealed 300 cc. of serosanguineous fluid in both pleural cavities and the peritoneal space. The heart weighed 350 gm. Despite striking dilatation of the right atrium and the right ventricle, no hypertrophy was noted. The tricuspid ring was dilated to a circumference of 17 cm. The area of division of the tumor was apparent immediately superior to the coronary sinus ostium. The liver weighed 1,700 gm. and showed striking congestion as did the adrenal glands and the spleen, which weighed 250 gm.

Microscopic sections of the cardiac muscle showed an increased amount of subepicardial fibrous connective tissue and scattered myocardial round cell infiltrates. Areas of thickening in the right atrial endocardium and scattered foci of loose myxomatous tissue resembling the excised tumor were found (Fig. 6B). Atelectasis and congestion were present in the lungs. Massive engorgement of the liver sinusoids and necrosis of parenchymal cells around the central veins were revealed.

Comment: This case illustrates several significant diagnostic criteria. Neither a history suggestive of acute myocarditis nor symptoms of left ventricular failure were present. The clinical findings were those of progressive, unexplained obstruction to the lesser circulation without evidence of underlying pulmonary disease. The holodiastolic murmur without presystolic accentuation, and a prominent third heart sound over the tricuspid area were suggestive of obstruction within the tricuspid or ventricular area. The possibility of a carcinoid tumor was eliminated by normal serial 5-hydroxyindoleacetic acid determinations. The high venous pressure and delayed circulation time also suggested a severe degree of intracavitary obstruction.

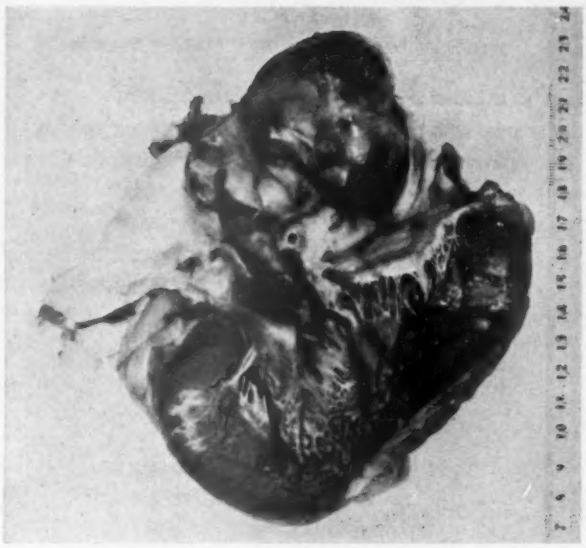


FIG. 7. Case 2. A 6 cm. pedunculated thrombus attached to the lateral wall of the left atrium fills the left atrial cavity. A fibrous scar suggestive of an old infarction is seen within the left ventricular myocardium.

CASE 2. A seventy year old white woman entered the hospital in coma after an episode of chest pain of thirteen hours' duration. Generalized cyanosis and dyspnea were present. The temperature was 99.2°F., the pulse 100 per minute and the blood pressure 84/60 mm. Hg. The neck veins were distended and moderate pulmonary edema was apparent. The heart was enlarged 2 cm. to the left of the midclavicular line and no left ventricular impulse was palpable. The rhythm was regular and the heart sounds were distant. A grade 1, soft, blowing midsystolic murmur was audible at the apex. The abdomen was obese and the liver enlarged 5 cm. below the right costal margin. The lower extremities were not tender or swollen.

Laboratory findings revealed a white blood cell count of 20,200 with 87 per cent polymorphonuclear leukocytes, 11 per cent lymphocytes and 2 per cent monocytes. The red blood cell count was 3.9 million per cu. mm.; the hemoglobin 12 gm. per cent and the corrected sedimentation rate (Wintrobe method) 50 mm. in one hour. The stool guaiac reaction was positive for blood.

The electrocardiogram demonstrated a normal sinus rhythm at a rate of 100 per minute with multiple atrial, nodal and ventricular premature contractions. The voltage was low and the P waves were broad and notched. The T waves and S-T segments were normal. The *roentgenogram* showed a large area of pulmonary infiltration superior and lateral to the right hilar region, calcification in the aortic arch and generalized cardiac enlargement.

Clinical Course: Pulmonary embolization and myocardial insufficiency were suspected. On the third hospital day, generalized abdominal pain and tenderness occurred without vomiting. The nonprotein nitrogen increased to 80 mg. per cent. On the sixth hospital day the patient died.

Postmortem examination revealed 100 cc. of clear yellow fluid in the pericardial cavity. The heart weighed 530 gm., the epicardium was smooth and glistening and an old myocardial infarction was demonstrated in the anterior portion of the left ventricle (Fig. 7). The mitral valve measured 8.5 cm. in circumference. The endocardium was thin, smooth and a large pedunculated thrombus 6 cm. in diameter was attached to the lateral wall of the left atrium. The peritoneal cavity contained 500 cc. of clear yellow fluid. The serosa of the small intestine was gray and mottled; the mucosa was hemorrhagic.

Microscopic sections of the mural thrombus showed degenerating blood elements in a fibrin net with proliferating fibroblasts and capillaries at the base. Sections of the middle lobe of the right lung revealed an area of parenchymal destruction suggestive of infarction. Sections of the small intestine showed massive hemorrhagic infarction. The aorta, mesenteric and iliac arteries showed thickening and atherosclerosis.

Comment: An intracavitary tumor or thrombus within the left cardiac chambers may liberate emboli to the systemic circulation. In this case, a large left atrial thrombus was found at autopsy. Death was due to an embolus and/or thrombus in the mesenteric artery, producing hemorrhagic infarction of the small bowel.

CASE 3. (Courtesy Dr. Harrison Shull). A sixty-two year old male teacher was admitted to Vanderbilt University Hospital for evaluation of progressive fatigue, nausea and vomiting of five hours' duration. Three years prior to admission unexplained acute myocardial insufficiency occurred. An "enlarged heart" and blood pressure of 160/100 mm. Hg were revealed. Progressive myocardial insufficiency developed. Eight months prior to evaluation, severe substernal pain occurred and the diagnosis of acute myocardial infarction was entertained. Although rest was enforced for six months, left ventricular failure continued and the patien' was transferred to another hospital. Phlebothrombosis developed in the left calf with subsequent right pulmonary infarction. After bilateral saphenous vein ligation anticoagulant therapy was instituted. Left cerebral infarction with right hemiplegia developed on the third postoperative day. For two years there was progressive development of numbness, tingling and weakness of the left hand. Two months prior to hospitalization the patient had episodes of syncope without pain but with profuse sweating. The blood pressure progressively decreased to 120/70 mm. Hg and a weight loss of 28 pounds occurred. After persistent severe abdominal

pain, nausea, vomiting and weakness, the patient was transferred to Vanderbilt University Hospital.

On physical examination, the temperature was 100.4° F., the blood pressure 115/90 mm. Hg, the pulse 80 and the respirations were 20 per minute. Left facial weakness and moderate venous engorgement were apparent. The chest was emphysematous and a few scattered inspiratory rales were audible over the lower right lung field. The left cardiac border was palpated in the fifth intercostal space at the anterior axillary line. There was an accentuated split pulmonic second sound and a grade 1, blowing holosystolic murmur at the apex. The liver was tender and enlarged 6 cm. below the right costal margin. Painful internal hemorrhoids and a moderate amount of peripheral edema were noted.

The electrocardiogram revealed an intraventricular conduction delay with a QRS duration of 0.10 second, S-T segment and T wave changes suggestive of digitalis effect and left ventricular enlargement. The *roentgenogram* revealed a prominent left ventricle with a cardiothoracic ratio of 19 : 33 cm.

Hospital Course: For five days, the patient had intermittent episodes of mental confusion, nausea, vomiting, weakness and peripheral numbness associated with cool, pale, moist skin, persistent fever, weak thready pulse and hypotension. Numbness and tingling of the right foot occurred on the fourteenth hospital day with disappearance of pulsations distal to the femoral artery. A continuous spinal block failed to prevent progressive cyanosis and gangrene of the lower third of the right leg. Gangrene of the fingers of the right hand and left foot became manifest. A rapid downhill course ensued and the patient died six weeks after admission to the hospital.

Autopsy Findings: The heart weighed 750 gm. with generalized enlargement and hypertrophy of all chambers. Although minimally atherosclerotic and widely patent coronary arteries were present, an old, healed posterior myocardial infarction was found. Multiple small thrombi were present in the right atrium and right ventricle. A mural thrombus occupying two-thirds of the left ventricular cavity was present. Embolization to the spleen, right iliac artery, right renal artery and cerebral vessels was noted. The cause of death appeared to be massive pulmonary infarction. Diffuse, generalized necrosis and fibrosis of the myocardium without specific cause was the most striking observation on microscopic examination.

Comment: In this instance, an underlying myocarditis with focal areas of necrosis appeared responsible for the multiple intracavitary mural thrombi with subsequent fatal pulmonary and systemic embolic manifestations. The large left ventricular mural thrombus and grossly impaired cardiac output contributed significantly to the terminal episode.

TABLE I

SYMPTOMS OF INTRACAVITARY CARDIAC TUMORS

ON RIGHT	ON LEFT
1) DUSKINESS OF SKIN	1) PROGRESSIVE DYSPNEA
2) CRAMPING OF LEGS	2) SUBSTERNAL PAIN
3) MARKED WEAKNESS	3) ORTHOPNEA
4) WEIGHT LOSS	4) PALPITATION
5) SWELLING OF ANKLES AND FEET	5) EMBOLI TO CEREBRAL, MESENTERIC, RENAL, AND PERIPHERAL ARTERIES
6) PULMONARY EMBOLI	6) VARIATION OF SYMPTOMS WITH CHANGE IN POSITION

1) DIZZINESS, SYNCOPE, CONVULSIONS
2) FEVER WITH NEGATIVE BLOOD CULTURES
3) HEMOPTYSIS
4) TACHYCARDIA AND ARRHYTHMIAS
5) GANGRENE OF NOSE AND TOES

Unexplained progressive myocardial insufficiency with subsequent embolic manifestations and low cardiac output without electrocardiographic demonstation of myocardial infarction are features compatible with myocarditis, fibroelastosis or intracavitary mechanical obstruction. Angiocardiography may differentiate these lesions.

COMMENTS

Intracavitary cardiac tumors and thrombi present specific symptoms and findings of obstruction to either the pulmonary or systemic circulation. Intracardiac lesions may be suspected if these findings are carefully evaluated.

Although intracavitary cardiac tumors obstructing the pulmonary circulation may be confused with obstructive pulmonary disease, constrictive pericarditis, tricuspid stenosis, the caval syndromes, myopericarditis and a carcinoid tumor, specific findings will differentiate this entity and angiocardiography can confirm the diagnosis. Intracavitary lesions obstructing the systemic circulation are most often confused with mitral stenosis, aortic stenosis or bacterial endocarditis.

Atrial myxomas frequently masquerade as mitral or tricuspid stenosis; over 90 per cent of the cases of myxomas of the left atrium were initially considered as rheumatic mitral stenosis. An "opening snap" was audible and recorded phonocardiographically in one instance of myxoma originating within the left atrium which had prolapsed through the mitral valve into

TABLE II

SIGNS OF INTRACAVITARY CARDIAC TUMORS

ON RIGHT	ON LEFT
1) TRICUSPID DIASTOLIC MURMUR	1) VARIABLE MITRAL DIASTOLIC MURMUR
2) LOUD, SNAPPING THIRD HEART SOUND	2) VARIABLE "OPENING SNAP" WITH CHANGE IN POSITION
3) NORMAL P_2 - NOT WIDELY SPLIT	3) APICAL PRESYSTOLIC THRILL
4) DISTENDED THROBBING NECK VEINS	4) ACCENTUATED, SPLIT P_2
5) HIGH VENOUS PRESSURE	5) ORTHOPNEA
6) PROLONGED CIRCULATION TIME	6) PROGRESSIVE UNEXPLAINED LEFT VENTRICULAR FAILURE
7) DILATED SUPERFICIAL COLLATERAL VEINS	7) POOR RESPONSE TO DIGITALIS
8) HEPATOMEGALY	
9) SEVERE HEMORRHOIDS IN THE YOUNG	
10) ASCITES	
11) PERICARDIAL EFFUSION	

1) LOW BLOOD PRESSURE
2) LOW PULSE PRESSURE
3) PLEURAL EFFUSION
4) PERIPHERAL GANGRENE
5) EDEMA

the left ventricular cavity.[43] Attacks of dizziness and syncope are common symptoms of intracardiac tumors and epileptiform convulsions and peripheral gangrene occur occasionally (Table I).[44–53] Embolic episodes to the cerebral, mesenteric, renal and peripheral arteries, associated with fever, cardiac murmurs, dyspnea, cyanosis and leukocytosis, may simulate subacute bacterial endocarditis.[54–64]

The physical signs produced by intracavitary cardiac tumors depend upon the size, location and degree of valvular obstruction (Table II). Progressive deterioration with either left, right or biventricular failure may develop. With change in the patient's position, an intracavitary tumor may produce sudden severe obstruction to the circulation by a "ball-valve" mechanism. Profound collapse or death may occur. With another change of position, however, immediate and dramatic spontaneous recovery can result.

Intracavitary cardiac tumors obstructing the right side of the heart produce the clinical picture of right ventricular failure. As mechanical obstruction progresses the neck veins may become painfully distended. The superficial veins of the face, thorax, abdomen and thighs dilate and the liver enlarges and may pulsate if tricuspid insufficiency exists. Ascites, severe hemorrhoids and edema are late manifestations. An unexplained high venous pressure with a significant delay of the arm-to-lung circulation time suggests the possibility of intracavitary obstruction.

Intracavitary tumors obstructing the systemic circulation produce signs simulating mitral or aortic valvular stenosis.[65] The diastolic murmur may be accentuated in late diastole, especially if the mitral orifice is obstructed; a third heart sound may be confused with the "opening snap" of mitral stenosis due to rheumatic fever. An apical presystolic thrill, a poor left ventricular impulse and an accentuated, widely split pulmonic second sound due to a tumor of the left atrium further encourage the physician to accept mitral valvular stenosis as the etiology of these findings. With change in the patient's position, these "classic" findings of mitral stenosis often disappear. As obstruction within the left side of the heart progresses, signs of left ventricular failure appear, often uncontrolled by digitalis.[66–68] Low blood pressure, pleural effusion, peripheral gangrene, edema and neurologic changes[69] are signs compatible with a poor cardiac output and may indicate obstruction to the right, the left or both sides of the heart (Table II).

Serial electrocardiographic changes, correlated with the clinical and roentgenologic findings, help to substantiate the diagnosis of an intracavitary cardiac lesion. With progressive obstruction to the right side of the circulation, the P waves become tall due to right atrial enlargement, the voltage of the ventricular deflections decreases due to impaired myocardial function and right bundle branch block usually occurs. An initial qR deflection in the right precordial leads with right bundle branch block suggests impairment of septal depolarization, tricuspid insufficiency or right atrial hypertrophy. This may be produced by a large right ventricular tumor or by infiltration of the septum.[70] Tumors involving the left side of the heart produce broad, notched P waves suggesting mitral stenosis and, as pulmonary hypertension develops, the electrical axis shifts to the right. Atrial arrhythmias with varying degrees of block may occur with either left or right atrial enlargement.[71–73] Complete heart block is most commonly observed when tumors invade the conduction system.[74,75]

Routine roentgenograms yield no diagnostic findings in the presence of intracavitary cardiac lesions. An unusual or irregular cardiac shadow in the roentgenogram, however, should alert the physician to this possibility.[76] Left

atrial myxomas result in roentgenographic findings similar to rheumatic mitral valvular disease, with left atrial enlargement, enlargement of the main pulmonary artery segment, pulmonary venous and arterial hypertensive changes and right ventricular hypertrophy. Over 370 instances of left atrial tumors or thrombi have been mistaken for mitral stenosis.[77–91]

Right atrial myxomas may simulate tricuspid valvular disease with right atrial and ventricular enlargement. The uncommon incidence of isolated tricuspid valvular disease, however, should arouse suspicion of a tumor. Calcification rarely occurs with myxomas. Other types of cardiac tumors are rare and reveal less specific radiographic manifestations. A primary malignant tumor of the heart has been diagnosed by pneumopericardium,[92] and the rare rhabdomyosarcoma is frequently associated with massive hemopericardium. Conceivably, a large lipoma could produce a perceptible radiolucent area reflecting the relatively low density of fat.

Angiocardiography is the most important diagnostic procedure for identification of intracavitary cardiac tumors. Low morbidity and mortality figures are associated with current contrast media and technics (one death in 3,100 consecutive examinations) and this examination should be performed whenever the possibility of a cardiac tumor exists.[93,94] Chamber-filling defects are clearly outlined and often diagnostic of a tumor. Atrial thrombi are usually irregular in outline; myxomas are usually smooth with frequent protrusion of the myxoma into the adjacent ventricle or valve ring.

Cardiac catheterization findings are available in several patients in whom the diagnosis of intracavitary cardiac tumors has been confirmed. This procedure, however, is usually not recommended. An obstruction of the outflow tract from the atria or ventricles is a consistent finding. Right atrial or ventricular tumors produce an elevated right atrial pressure with the lowest pressure just prior to ventricular contraction, suggestive of an underlying "ball-valve" mechanism.[4] If the tumor is large the operator may experience difficulty in passing the catheter around the obstructing lesion. Extreme caution must be exercised during catheterization as the catheter itself may cause complete obstruction.[95] In the presence of a right ventricular tumor the right atrial pressure curve may demonstrate the lowest point of pressure in diastole just before atrial contraction. This could be a differential diagnostic feature because with tricuspid stenosis the atrial pressure should be rising at this point.[11] The systolic pressure rise with left atrial tumors may be rapid in the left atrial pressure tracings with the *C* wave higher than the *V* wave. The X descent is usually well preserved.[8] Reduced cardiac output is noted with either right or left intracavitary tumors.

The pathology of cardiac tumors and thrombi is controversial.[38,96,97] Prichard[38] published an excellent pathologic report in which the theories of pathogenesis of tumors of the heart are discussed. Although some pathologists regard myxomas as organized thrombi, others assume a neoplastic origin. Mahaim's[98] differentiation of a myxoma from a thrombus is generally accepted. Thus, the so-called myxoma of the heart is established as a nosologic entity but its pathogenesis remains disputed. The similarity of myxomas and fibroblasts growing in tissue culture has frequently been noted[99] and one must not ignore the vasculature of the tumor when making such comparisons. In describing myxomas areas of necrosis and hemorrhage are frequently noted. It is often difficult to distinguish between an area of hemorrhagic necrosis in fibrous tissue and a blood clot undergoing organization.

Although the tumor found in the first patient presented here satisfies the criteria of a myxoma, the evidence of pericarditis and myocarditis was impressive. However, it is possible that the round cell infiltrate in the right ventricular myocardium could have been produced from trauma by the tumor. The finding of other myxomas in the endocardium is unusual and has not previously been reported.

Summary

Intracavitary cardiac tumors or thrombi are rarely recognized before death. Now that successful surgical methods for removal of these lesions are available, early clinical recognition is important. Three instances of intracavitary cardiac obstructive lesions are presented in an attempt to further elucidate the clinical characteristics, diagnostic methods, pathology and surgical treatment of these lesions.

Angiocardiography is the most important single diagnostic procedure for identification of intracavitary cardiac tumors and should be undertaken whenever the possibility of such a lesion exists.

Addendum

Since the submission of this report we have encountered two additional patients, a fifty-two year old man and a forty-six year old woman, with massive thrombosis of the left atrium in association with mitral stenosis. Both patients manifested evidence of previous systemic embolization. Removal of the thrombotic material and adequate opening of the mitral valve were successfully accomplished in both patients by utilizing a pump oxygenator for temporary cardiopulmonary bypass. The large atrial thrombus in the fifty-two year old man appeared to be partially responsible for obstruction of the mitral valve. Both patients continue to do well in the postoperative period.

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Blood Gas Changes Following Priscoline Administration in Mitral Stenosis and Chronic Lung Diseases*

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THE ADMIXTURE of venous blood in the arterial circulation in normal individuals is thought to be caused by perfusion of non-ventilated areas of lung and by true anatomic intrapulmonary shunts.[1,2] This venous admixture was found to be increased in several diseases.[3–5] In the present investigation the gas content of the arterial blood was studied after administration of Priscoline,®† on the assumption that this drug, causing vasodilation and increased cardiac output,[6,7] may also induce changes in the amount of venous admixture. The experiments were performed on normal individuals and on patients with mitral stenosis and chronic lung diseases.

MATERIAL AND METHODS

Twenty-two normal subjects, forty-seven patients with mitral stenosis of varying severity and fourteen patients with chronic pulmonary disease (mainly bronchiectasis and advanced tuberculosis), were examined in a fasting state.

In all these patients a No. 18 Cournand needle was inserted into the brachial artery. After ten minutes' rest an arterial blood sample was taken and the oxygen (O_2) and carbon dioxide (CO_2) contents were determined immediately by the Van Slyke-Neill method. Duplicate samples were required to tally within 0.2 volume per cent. Twenty-five mg. of Priscoline were then administered over a three minute period through an antecubital vein of the opposite arm. Ten minutes after the end of the injection a second arterial blood sample was taken and the blood gases were again determined. The oxygen carrying capacity of both samples was also determined. Special attention was given to maintain complete rest of the patient and to avoid emotional reactions during the period between the two examinations. Subjects showing any such reactions were excluded from the series.

RESULTS

Group I. Normal Subjects: In the group of twenty-two subjects without cardiopulmonary disease (Table 1) the average O_2 content in the resting condition was 18.52 (±0.69) volumes per cent‡ and the average value of O_2 saturation was 95.9 per cent. Ten minutes after administration of Priscoline twelve individuals showed a decrease in oxygen content, from an average of 19.08 volumes per cent to an average of 18.00 volumes per cent. The respective change in O_2 saturation was a decrease from 97.9 to 95.1 per cent. Six individuals showed variations in O_2 content less than 0.2 volume per cent while four patients showed an increase in O_2 content after administration of the drug from an average of 17.99 to 18.73 volumes per cent (from 92.5 to 96.0 per cent saturation). The average O_2 content of the whole group dropped to 18.31 (±0.38) volumes per cent and the O_2 saturation dropped to 95.0 per cent. The t value§ of the change in O_2 content was 1.489, showing the change to be nonsignificant.

The average CO_2 content of the whole group in the resting condition was 47.33 (±2.19) volumes per cent. In eleven subjects following administration of Priscoline the CO_2 content rose from an average of 48.14 to an average of 48.95

‡ The figure appearing after the sign ± is twice the standard error estimate.

§ The t value was computed as required for the Student-Fischer test on paired observations. Whenever nonsignificance is stated, it refers to the P = 0.05 significance level.

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† Benzyl-imidazoline hydrochloride.

TABLE I

Oxygen and Carbon Dioxide Content of the Arterial Blood in the Resting State and Ten Minutes after Intravenous Administration of Priscoline in the Various Groups

Groups	No. of Cases	O_2 Content			Average O_2 Content (vol. %)		t Value
		Decrease	No Change	Increase	Resting	After Priscoline	
I. Normals	22	12	6	4	18.52 (±0.69)	18.31 (±0.38)	1.489
II. Mitral stenosis	47	38	6	3	16.94 (±0.91)	16.48 (±1.67)	5.582
III. Chronic lung disease	14	13	..	1	17.91 (±1.25)	17.13 (±1.08)	4.699
		CO_2 Content			Average CO_2 Content (vol. %)		
I. Normals	22	4	7	11	47.33 (±2.19)	47.71 (±2.35)	−1.801
II. Mitral stenosis	47	15	20	12	45.85 (±1.49)	45.49 (±3.36)	1.747
III. Chronic lung disease	14	2	4	8	47.50 (±2.96)	48.31 (±4.50)	0.947

volumes per cent; in seven patients the CO_2 content varied by less than 0.2 volume per cent and in four patients there was a drop in the CO_2 content after the drug, from an average of 46.17 to an average of 45.71 volumes per cent. The average CO_2 content of the whole group after administration of Priscoline was 47.71 (±2.35) volumes per cent; the t value was −1.801, showing a nonsignificant change.

Group II. Mitral Stenosis: In the group of forty-seven patients with mitral stenosis (Table 1) the average O_2 content in the resting condition was 16.94 (±0.91) volumes per cent and the average O_2 saturation 96.6 per cent. In thirty-eight patients a drop in the O_2 content occurred from an average of 17.00 to an average of 16.37 volumes per cent (a drop from 97.1 to 93.5 per cent in the O_2 saturation); in six patients the change in the O_2 content after the administration of the drug was less than 0.2 volume per cent, while three patients showed a rise in the O_2 content from an average of 15.92 to 16.52 volumes per cent (from 92.5 to 96.0 per cent saturation). The average O_2 content of the whole group ten minutes after the administration of Priscoline dropped to 16.48 (±1.67) volumes per cent. The t value of the change in the whole group was 5.582, proving the change to be significant ($P < 0.001$).

The resting average CO_2 content of the whole group was 45.85 (±1.49) volumes per cent. Twelve patients showed a rise in the CO_2 content after the administration of Priscoline, from an average of 45.84 to an average of 46.65 volumes per cent; in twenty patients the CO_2 content remained within the limits of ±0.2 volume per cent following injection of the drug, while fifteen patients showed a decrease in the CO_2 content, from an average of 45.91 to 44.67 volumes per cent. The average CO_2 content of the whole group ten minutes after the administration of the drug was 45.49 (±3.36) volumes per cent; a change not significant according to our calculation (t = 1.747).

Group III. Chronic Lung Disease: Fourteen patients with chronic lung disease were examined (Table 1). The average O_2 content of the whole group in the resting state was 17.91 (±1.25) volumes per cent and the O_2 saturation 94.1 per cent. Thirteen of the fourteen patients showed a drop in the O_2 content following administration of Priscoline, and the average value decreased to 17.13 (±1.08) volumes per cent (91.6 per cent saturation). The t value of 4.699 proved a significant change ($P < 0.001$).

The average CO_2 content of the whole group was 47.50 (±2.96) volumes per cent. In eight patients following the administration of the drug the CO_2 content showed a rise from an average of 49.88 to 52.09 volumes per cent. In four patients the change in the CO_2 content remained within the limits of ±0.2 volume per cent, while two patients showed a drop in the CO_2 content, from an average of 44.76 to an average of 42.87 volumes per cent. The average CO_2 content of the whole group showed a rise to 48.31 (±4.50) volumes per cent, which change was proved to be nonsignificant by statistical evaluation ($t = 0.947$).

Comments

Significance of Results in Normal Subjects: The existence of venoarterial shunts in normal individuals has been demonstrated by anatomic studies,[8] by the presence of a consistent O_2 gradient between the alveolar air and the arterial blood[2] and by the passage of glass spheres through the pulmonary circulation.[10] The amount of blood shunted through these vessels is estimated to be about 2 per cent of the cardiac output.[11] The aim of this investigation was to influence only one of the factors responsible for the maintenance of normal blood gas exchange, viz., the distribution of blood flow within the pulmonary vascular bed, and thus to increase the venous admixture. In these experiments we used Priscoline, a drug known to cause vasodilation and a rise in cardiac output and pulmonary blood flow. Although we observed a decrease in the arterial O_2 content following administration of the drug in about 50 per cent of normal individuals, statistical evaluation of this change proved it to be nonsignificant. A drop in arterial O_2 saturation following administration of vasodilator drugs in normal subjects was observed by Niden and Barclay[11] and alteration in ventilation-perfusion ratio and opening up of anatomic shunts are suggested to be responsible for this change. A similar conclusion was reached by Jose and Milnor[5] who used a different technic for the demonstration of pulmonary arteriovenous shunts in normal subjects. These authors reported an increase of the arterial O_2 saturation by an average of 1.2 per cent during performance of the Valsalva maneuver, and explained this phenomenon by a decrease in blood flow through these intrapulmonary shunts secondary to the hemodynamic effects of this maneuver.

Significance of Results in Mitral Stenosis: In patients with mitral stenosis the drop of the O_2 content after administration of Priscoline was more frequently observed than in the normal individuals. It was demonstrated in about 80 per cent of the cases, and the decrease was found to be statistically significant. The existence of an increased venous admixture in patients with mitral stenosis was reported by several authors[12–14] and was explained by the difficulty of diffusion of gas in areas where the alveolocapillary wall is thickened, fibrotic or edematous. Priscoline was shown to cause pulmonary vasodilation in patients with mitral stenosis with a concomitant rise in cardiac output,[15] and the administration of it in these experiments seemed to increase the perfusion of the poorly ventilated areas, leading to the drop in arterial O_2 saturation. Furthermore, the true arteriovenous shunts are also more developed in mitral stenosis[13] and Priscoline seemed to increase the flow through these anastomotic vessels. These results, however, do not permit any conclusion to be drawn as to whether the blood flow through poorly ventilated areas or the flow through the true anastomotic channels is more affected by the vasodilation and/or the increased cardiac output caused by the drug. In only twelve patients a rise in the CO_2 content was observed together with a decrease of the O_2 content of the arterial blood.

Although pulmonary hypertension was suggested to increase the size of the anastomotic vessels in the lungs during experimental conditions,[16] no correlation could be detected by us between the height of the pulmonary arterial pressure and the amount of venous admixture at rest in fifteen patients studied by right heart catheterization. Furthermore, we also could not find a direct relationship between the height of the pulmonary arterial pressure and the decrease of arterial O_2 saturation after administration of Priscoline. A lack of correlation between the amount of venous admixture and the height of the pulmonary arterial pressure in patients with mitral stenosis was also reported by Fowler et al.[14] Recent investigations of patients with mitral stenosis have shown that administration of acetylcholine causes a drop in the arterial O_2 saturation[17] of similar magnitude to that observed by us following the administration of Priscoline. As to the mechanism of this change, alterations in ventilation-perfusion ratio and a direct effect on the anastomotic shunt vessels have been suggested.

Significance of Results in Chronic Lung Disease: The results obtained in the group of patients with chronic lung disease were more uniform than those obtained in patients with mitral stenosis. In thirteen of the fourteen patients examined a marked decrease of the O_2 content was found following the administration of Priscoline. Frequently some perfusion of the destroyed lung tissue in these patients still exists, causing slight arterial O_2 unsaturation at rest. Increasing pulmonary blood flow caused by Priscoline is followed by a further drop of the oxygen content of the arterial blood and, in some cases, a rise in the CO_2 content. A recent study of Halmagyi and Cotes[18] performed on patients with chronic pulmonary disease revealed also a decrease of the oxygen saturation following drugs which increase the cardiac output and/or reduce the pulmonary vascular resistance.

Summary

The O_2 and CO_2 content in the arterial blood of normal individuals and of patients with mitral stenosis and with chronic lung disease were examined in the resting state and ten minutes after the intravenous administration of Priscoline. In about half of the normal individuals a drop in the O_2 content was observed after the drug; however, this change was statistically nonsignificant. In the majority of patients with mitral stenosis and with chronic pulmonary disease a statistically significant drop of the O_2 content was observed while changes in the CO_2 content varied. The observed drop in the arterial O_2 content after administration of a drug known to cause vasodilation and augmented cardiac output is thought to be brought about by increased perfusion of poorly ventilated areas in the lungs and/or by increased flow through true intrapulmonary shunt vessels.

Acknowledgment

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A Ballistocardiographic Study of Left Bundle Branch Block*

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RECENTLY, AN ultra-low frequency acceleration ballistocardiograph has been developed which records accurate and reliable information about cardiovascular dynamics.[1] Specific deflections on the ballistocardiogram have been correlated with detailed events within the systolic portion of the cardiac cycle. Left bundle branch block is a unique clinical example of a conduction block easily demonstrable on the electrocardiogram. It is known that altered conduction and depolarization can influence the pattern of myocardial function.[2] The purpose of this study is to explore with the ballistocardiogram the cardiovascular dynamics in ten cases of left bundle branch block.

METHODS

The ballistocardiograph used in the present study was a slight modification[3,4] of the Reeves ultra-low frequency acceleration model.[1] A simultaneous ballistocardiogram, electrocardiogram (lead II) and carotid pulse tracing were recorded on a four-channel Sanborn poly-viso cardiette. The method of analyzing the recorded pattern from this ballistocardiograph has been described previously.[5] The subjects were ten men from thirty-three to seventy-five years of age. All were part of a cardiac evaluation at the Cardiac Clinic, U. S. Naval School of Aviation Medicine, Pensacola, Florida. The diagnosis of left bundle branch block was based upon a twelve lead standard electrocardiogram which demonstrated a QRS interval greater than 0.12 second in the frontal plane, an M-shaped QRS complex in leads I and V_6, initial and terminal 0.04 second QRS vectors pointing leftward and posteriorly and associated secondary T wave changes. The diagnosis of left bundle branch block was confirmed in all ten cases by a vectorcardiogram.

RESULTS

The time duration from the electrocardiographic Q wave to the onset of the carotid upstroke ($Q–C_u$) generally was 0.14 second or greater in all cases of left bundle branch block (Table I). The ballistocardiogram in each of these subjects showed a prominent interruption in the HIJ complex, the so-called I^+ deflection referred to by Reeves.[1] A schematic diagram elucidating the nomenclature of the I, I^+ and I' deflections to be used in the present study is presented in Figure 1.

The measurement of the various time intervals relating the Q wave of the electrocardiogram to the interruptions in the ballistocardiographic HIJ complex (I, I^+, I') and to the carotid upstroke are presented in Table I. The delay between the onset of left ventricular ejection (LVE) and the recorded carotid upstroke was calculated indirectly from a number of papers in the literature[1,6,7] and averaged about 0.02 second. With the use of this figure the onset of left ventricular ejection was related to the ballistocardiographic tracing. Left ventricular ejection began in two of the cases coincident with the I deflection, in six of the cases between the I and I^+ wave, and in one case coincident with the I' deflection. The proximity of the interruption in the ballistocardiographic HIJ complex to the onset of left ventricular ejection is evident.

Although the records of all patients with left bundle branch block had a prominent I^+ deflection, there was some variation in the position of this wave relative to other deflections in the HIJ complex. In Figure 2 it can be seen

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TABLE I

Time Relations Between the Simultaneously Recorded Electrocardiogram, Ballistocardiogram and Carotid Pulse Tracing in Ten Cases of Left Bundle Branch Block

Case No.	Age (years)	Time of Intervals (sec.)						Onset of LVE*
		Q–H	H–I	H–I$^+$	H–I′	H–C_a	Q–C_a	
1	33	0.08	0.08	0.10	0.12	0.10	0.18	I
2	37	0.10	0.04	0.06	0.08	0.07	0.17	I–I$^+$
3	40	0.12	0.06	0.08	0.10	0.09	0.21	I–I$^+$
4	42	0.09	0.05	0.08	0.10	0.10	0.19	I$^+$
5	50	0.08	0.08	0.13	0.14	0.12	0.20	I–I$^+$
6	57	0.06	0.05	0.07	0.08	0.09	0.14	I–I$^+$
7	60	0.04	0.06	0.12	0.16	0.12	0.16	I–I$^+$
8	64	0.10	0.03	0.07	0.10	0.07	0.17	I–I$^+$
9	64	0.09	0.04	0.07	0.11	0.06	0.15	I
10	75	0.05	0.07	0.09	0.11	0.13	0.18	I′
Average	52.2	0.08	0.06	0.09	0.11	0.10	0.17	...

* Indicates the position of the calculated onset of left ventricular ejection (LVE) relative to the ballistocardiographic (I, I$^+$, I′) deflections.

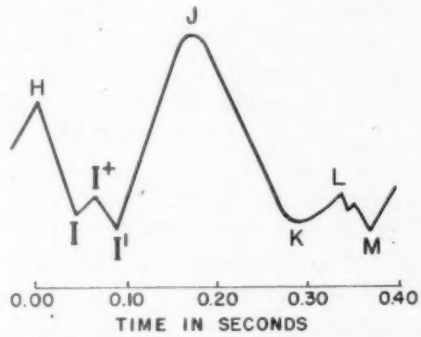

FIG. 1. Diagrammatic labeled illustration of the ultra-low frequency acceleration ballistocardiogram.

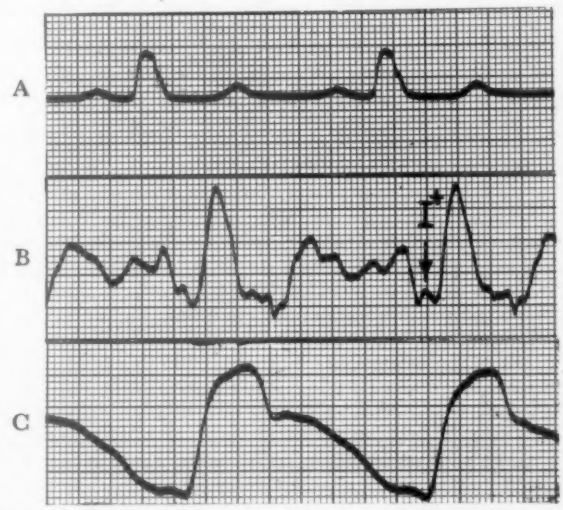

FIG. 2. Case 2. Simultaneous electrocardiogram (A), ballistocardiogram (B) and carotid pulse tracing (C). The I$^+$ deflection is synchronous with the carotid upstroke and occurs during the terminal portion of the HI segment. Paper speed in this and subsequent figures is 50 mm. per second.

that the I$^+$ deflection is inscribed during the terminal portion of the recorded HI segment and is coincident with the carotid upstroke. An abortive I$^+$ deflection is seen in two of the three ballistocardiographic complexes in Figure 3. In the ballistocardiographic tracing presented in Figure 4, the I$^+$ deflection is followed by a concave scalloping of the initial portion of the I′J segment. In this subject's record (Case 10) the I$^+$ deflection precedes the carotid upstroke by 0.03 to 0.04 second. However, the calculated onset of left ventricular ejection is coincident with the I′ deflection. A late occurring I$^+$ wave (0.13 second after H) is pre-

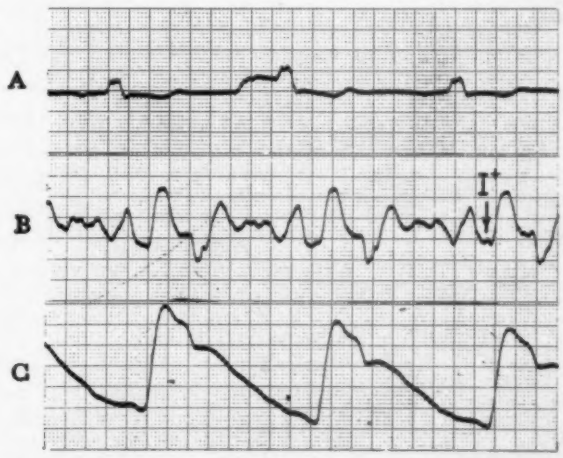

FIG. 3. Case 3. Simultaneous electrocardiogram (A), ballistocardiogram (B) and carotid pulse tracing (C). There is an abortive I$^+$ deflection discernible at the bottom of the HI segment of the ballistocardiogram. This I$^+$ deflection is coincident with the recorded carotid upstroke.

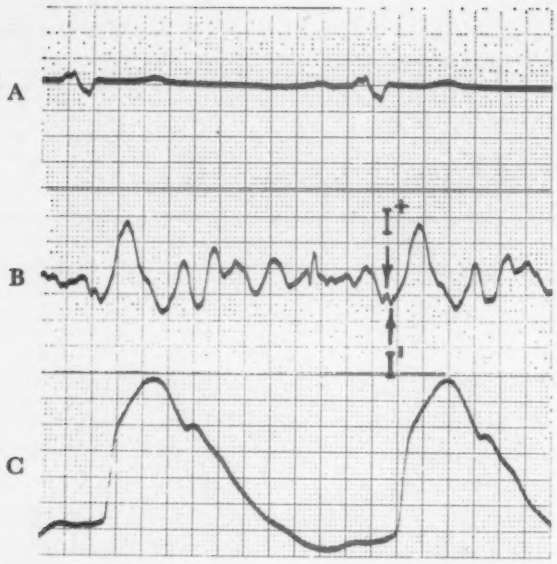

FIG. 4. Case 10. Simultaneous electrocardiogram (A), ballistocardiogram (B) and carotid pulse tracing (C). The I^+ deflection in the ballistocardiogram precedes the carotid upstroke by 0.04 second. The I^+I' deflection is followed by concave scalloping of the I'J segment.

sented in Figure 5; in this record the I^+ wave is inscribed at the time of the carotid upstroke.

Routine analysis of the ballistocardiograms in terms of wave amplitudes and time durations between various deflections is presented in Table II. Eight of the ten subjects had ballistocardiographic tracings with one or more abnormal amplitude measurements as defined by criteria previously established in a normal, healthy, male population.[5]

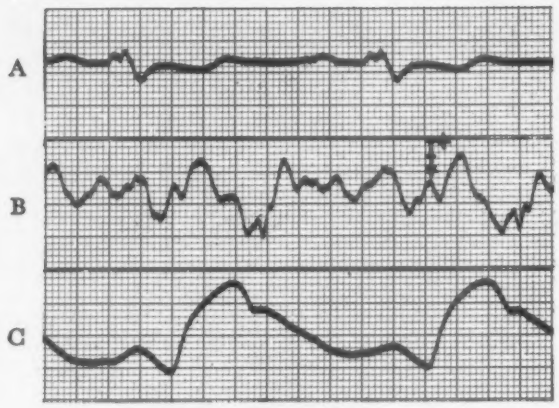

FIG. 5. Case 5. Simultaneous electrocardiogram (A), ballistocardiogram (B) and carotid pulse tracing (C). The I^+ deflection in the ballistocardiogram is coincident with the carotid upstroke and is inscribed 0.13 second after the H deflection.

Intermittent Left Bundle Branch Block: The electrocardiogram of one subject (Case 6) revealed intermittent left bundle branch block. The ballistocardiogram consistently showed the same pattern regardless of whether conduction block was present or not (Fig. 6). Detailed analysis of this subject's ballistocardiogram during left bundle branch block and during normal conduction is presented in Table III. The variable block did not alter the onset of left ventricular ejection relative to the electrocardiographic Q wave, for the $Q–C_u$ time interval remained constant. The individual ballistocardiographic measurements were essentially the same in the two different con-

TABLE II

Analysis of the Ballistocardiographic Pattern in Ten Cases of Left Bundle Branch Block

Case No.	Heart Rate	Ballistocardiographic Measurements						
		HI Angle (degrees)	Amplitude (mm.)			HK/HI	Time (sec.)	
			HI	HJ	HK		H–Jp	H–L
1	50	31.8	8.7	6.7	11.7	1.34*	0.20	0.39
2	80	13.3	8.7	9.7	7.3	0.83	0.17	0.33
3	71	18.8	9.0	4.3	6.7	0.74	0.18	0.30
4	69	10.3	13.0	4.0*	11.7	0.90	0.18	0.35
5	75	23.3	7.0*	2.7*	9.9	1.41*	0.20	0.37
6	71	12.7	11.3	3.3*	10.3	0.91	0.17	0.34
7	71	19.7	9.7	5.7	14.7	1.52*	0.23	0.35
8	68	17.8	4.7*	9.0	8.3	1.76*	0.16	0.32
9	77	8.7	11.0	0.0*	16.0	1.46*	0.17	0.33
10	53	29.5	6.0*	9.7	7.7	1.28*	0.20	0.41

* Indicates an abnormal ballistocardiographic measurement as defined by previously established criteria.[5]

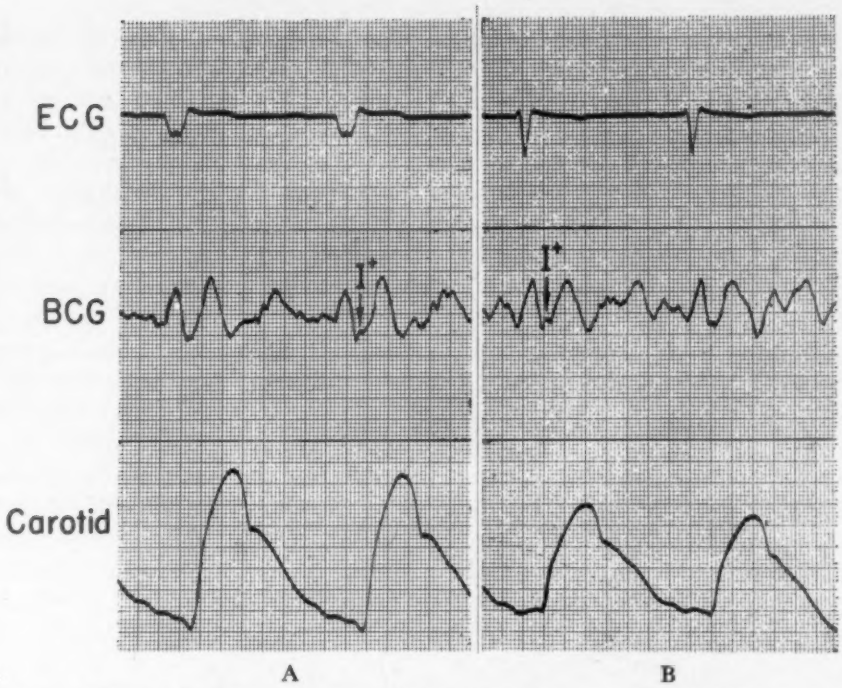

FIG. 6. Case 6. Ballistocardiograms during (A) left bundle branch block and (B) normal conduction. The ballistocardiographic pattern remains essentially the same regardless of the conduction state. Also, the I^+ deflection is discernible in each tracing.

duction states. Although the H point appeared to be inscribed slightly earlier during the conduction block (Q–H in left bundle branch block = 0.06 second; Q–H in normal QRS = 0.07 second), the time interval between the I, I^+ and I′ deflections relative to the electrocardiographic Q wave remained the same. The calculated onset of left ventricular ejection (0.02 second before the carotid upstroke) fell between the I and I^+ deflections during both left bundle branch block and normal conduction. It appears that the basic ballistocardiographic pattern in this subject was not influenced by the presence or absence of left bundle branch block on the electrocardiogram.

TABLE III

Analysis of the Ballistocardiographic Patterns in a Subject (Case 6) with Intermittent Left Bundle Branch Block

Ballisto-cardiographic Measurements	Left Bundle Branch Block	Normal Conduction
Heart rate	71.0	71.0
HI angle (degrees)	12.7	11.0
Amplitude (mm.)		
HI	11.3	10.3
HJ	3.3*	0.0*
HK	10.3	12.0
HK/HI	0.91	1.16*
Time (sec.)		
H–Jp	0.17	0.17
H–L	0.34	0.32
Q–H	0.06	0.07
H–I	0.05	0.04
$H–I^+$	0.07	0.06
H–I′	0.08	0.07
$H–C_u$	0.08	0.07
$Q–C_u$	0.14	0.14

* Indicates an abnormal ballistocardiographic measurement as defined by previously established criteria.[6]

COMMENTS

A consistent ballistocardiographic pattern has been described in ten patients with left bundle branch block. In each case the ballistocardiogram was interrupted by an I^+ deflection which was correlated with the delayed onset of left ventricular ejection. Correlations of cardiovascular events with the specific ballistocardiographic deflections were made with the method used by Reeves[1] in interpreting the forces responsible for the ballistocardiographic pattern. Reeves believed that the HI wave represented the recoil force from cardiac ejection. Since left ventricular ejection begins about the time of the I^+ wave, then the HI segment preceding the I^+ deflection must represent recoil only from right ventricular ejection. Left ventricular

ejection would produce a footward recoil force in the same direction as the right sided ejection; it is likely that the I^+ I' segment represents part of this left sided ejection force. During the inscription of the $I'J$ segment in left bundle branch block there are at least two major opposing forces present. That is, the impact of blood against the pulmonary artery from right sided ejection would produce an $I'J$ upstroke due to a headward force; continued left ventricular ejection after the I^+I' segment would tend to inscribe a downward deflection in the $I'J$ segment due to the continued footward recoil force. The interaction of these opposing forces in the initial portion of the $I'J$ segment may be responsible for the concave scalloping of this wave seen in Figure 4 and frequently observed in the ten cases of left bundle branch block. The cardiovascular force responsible for the $I\text{-}I^+$ deflection is not clear. Reeves has suggested that the impact of ejected blood against the aortic valve may produce a small headward force which would just precede the recoil force of left ventricular ejection. It is possible that the $I\text{-}I^+$ deflection represents the force responsible for the opening of the aortic valve.

Ventricular Asynchronism in Left Bundle Branch Block: The clarity with which the I^+ deflection was recorded may have been determined in large part by the asynchronous ventricular ejection. This asynchrony is represented by the time differential between the onset of the HI (right ventricular) and I^+I' (left ventricular) deflections. It should be mentioned that asynchronous ventricular ejection in all cases of left bundle branch block is still open to question. Samet et al.,[8] using an electrokymographic technic, demonstrated delayed mechanical ejection from both sides of the heart in the majority of cases of left bundle branch block. However, asynchronous ventricular ejection was present in only one-third of their cases. In contrast to these findings, Ellinger et al.[7] and Wolferth and Margolies[9] demonstrated a consistent ventricular asynchronism in left bundle branch block similar to the results observed in the present study.

The I^+ deflection recorded in the ultra-low frequency acceleration ballistocardiogram in this study may represent the same physiologic event as the notched J wave reported by other investigators studying the ballistocardiogram in left bundle branch block.[10,11] The notched J wave was recorded with ballistocardiographic technics which measured displacement and velocity on high frequency pickups; thus, it cannot be compared directly with the I^+ deflection seen in the present study. However, the fact that an interruption in the systolic ballistocardiographic complex occurred in left bundle branch block with both technics is significant.

Myocardial Function in Left Bundle Branch Block: In the majority of cases of left bundle branch block the probable cause is coronary artery disease. In the present series of ten cases there were eight subjects with abnormal ballistocardiographic records indicative of accelerated cardiovascular aging.[5] This finding strengthens the possible relationship between accelerated cardiovascular aging as determined by the ballistocardiogram and coronary artery disease. There were two subjects whose records met the ballistocardiographic criteria of normality.[5] The finding of both normal and abnormal ballistocardiographic patterns can be explained by the fact that a block in the conducting bundle *per se* does not necessarily impair cardiac contraction.[12] The extent of coronary artery disease in left bundle branch block may be variable; therefore, the block may indicate only a small scar in the conducting system or can be associated with extensive ischemic (coronary) heart disease.[13] In the former case one would expect only minimal alteration in the pattern of ventricular contraction and it is reasonable to expect that the ballistocardiogram would be normal; in the latter case there would be gross alteration in myocardial function and an abnormal ballistocardiogram would not be surprising. These assumptions are in agreement with those of Dock et al.[12] who believe that when abnormal ventricular function is seen in left bundle branch block it probably indicates intrinsic myocardial disease superimposed on the conduction block.

The one subject with intermittent left bundle branch block demonstrates clearly some of the relationships between the electromechanical events in this condition. Regardless of whether there was a normal QRS or a conduction block, the ballistocardiogram remained essentially unchanged and the I^+ deflection as well as the abnormal pattern persisted. These findings emphasize that the I^+ wave is not specific for left bundle branch block but is probably indicative of delayed left ventricular ejection. Also, the abnormal ballistocardiographic pattern is independent of the conduction block and

probably reflects disordered cardiac function on the basis of ischemic heart disease.

Summary

Ten subjects with left bundle branch block were studied with the ultra-low frequency acceleration ballistocardiograph. A prominent interruption (I^+ deflection) was present in the early systolic portion of the ballistocardiographic complex in all ten patents. This I^+ deflection was correlated with the delayed onset of left ventricular ejection.

An abnormal ballistocardiographic pattern indicative of accelerated cardiovascular aging was present in eight of the ten subjects and was attributed to associated coronary artery disease producing altered myocardial function.

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Observations on Coronary Sinus Rhythm and Its Mechanism*

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CORONARY SINUS RHYTHM is a form of retrograde atrial activation identified by inverted P waves in leads II, III and aVF with a P-R interval greater than 0.12 second (Fig. 1). Since lead I may register a flat, diphasic or upright P wave, the mean manifest frontal P axis will fall between −31° and −90° (Fig. 2). This sector lies within the range of A-V nodal rhythms, but the latter are distinguished by shortened P-R intervals.

CLINICAL AND ELECTROCARDIOGRAPHIC DATA

In two series of 10,000 electrocardiograms each, only fifteen[1] and seventeen[2] instances of coronary sinus rhythm could be identified. The incidence was apparently higher among our patients: there were nine cases among 3,500 consecutive tracings. The clinical and electrocardiographic data for these are summarized in Table I.

P axes in our cases fell between −60° and −90° and P-R intervals varied from 0.14 to 0.20 second. The QRS interval was always normal. There was no relation of this rhythm to any range of QRS orientation, heart rate, blood pressure or the use of drugs. There was no predilection of sex and the age range (thirty-nine to seventy-seven years) reflects that of our hospital population. Although six of nine patients had pulmonary emphysema and only three had manifest heart disease, the small sample should not permit etiologic conclusions. (A younger series of eight patients [ages twenty-four to fifty-five years] included only one with emphysema and two with heart disease.[3]) Serum electrolytes were within normal limits except in Case 8 (potassium was 8 mEq./L. terminally).

In each of five subjects who had more than a single electrocardiogram, one or more supraventricular dysrhythmias were seen (Table I); coronary sinus rhythm was always a transient phenomenon and all five showed sinus rhythm at some time. In every instance the P-R interval was shorter during coronary sinus rhythm. Three exhibited both coronary sinus rhythm and sinus rhythm in the same tracing (Fig. 3).

COMMENTS

Experimental Production of Coronary Sinus Rhythm: Coronary sinus rhythm may be produced in normal persons by breathing 100 per cent oxygen.[4] It may be elicited or changed to sinus rhythm by amyl nitrite inhalation, carotid sinus stimulation or an ectopic beat[5] (Fig. 3A). Partial injury of the sinus node will be followed by coronary sinus rhythm, while complete destruction of the sinus node produces typical A-V nodal rhythm.[3,5,6] Warming the coronary sinus region epicardially or via the coronary sinus vein in dogs will induce coronary sinus rhythm, while endocardial warming results in apparent "middle nodal" rhythm.[6]

Site of Pacemaker: Experiments with atrial models[7] have demonstrated that impulses originating from the anterior margin of the junction of the inferior vena cava and right atrium produce negative P waves in leads II, III and aVF. Esophageal leads in a single case of coronary sinus rhythm showed that the pacemaker lay in "the midportion of the right atrium between the A-V node and the sinus node."[3] These loci correspond to the area of the coronary sinus ostium which lies within atrial territory but contains specialized conducting tissue in contact with the A-V node. The fact that such tissue lies on its posterior aspect may account for the ineffectiveness of

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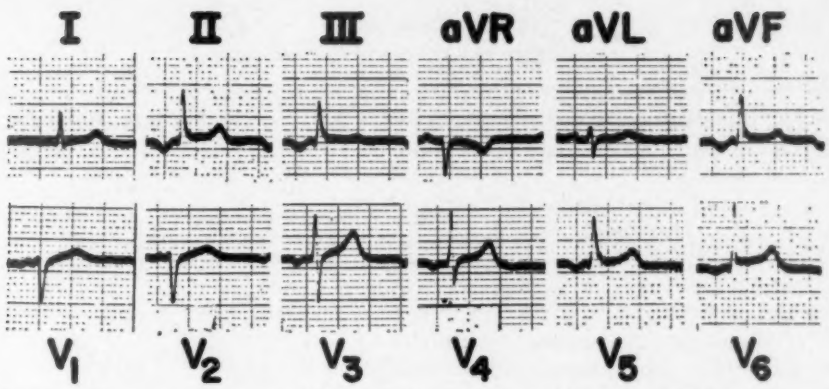

FIG. 1. Case 4. Coronary sinus rhythm. P wave inversions in leads II, III, aVF and V_1 to V_6. These are symmetrical in all but leads V_1 and V_2 where the predominant deflection is negative but there is terminal positivity. Mean frontal axes: P = −90°; QRS = +60°; T = +40°. P-R interval = 0.14 second. Apart from the ectopic pacemaker the tracing is within normal limits.

endocardial (vs. epicardial) warming in the experimental production of coronary sinus rhythm.[6]

Even when a probable site of origin is strongly suggested, the combination of characteristics of retrograde atrial activation with a normal P-R interval presents alternate possibilities. Langendorf, Simon and Katz[8] observed a case in which coronary sinus rhythm occurred in a patient with first degree A-V block and concluded that the mechanism represented A-V nodal rhythm with antegrade block. Considerable evidence suggests that this is not true of the majority of patients. No such instances were noted among our patients and other observers have failed to record delayed A-V conduction during orthograde atrial activation. The production of coronary sinus rhythm by amyl nitrite or 100 per cent oxygen and the smooth, spontaneous transition between cor-

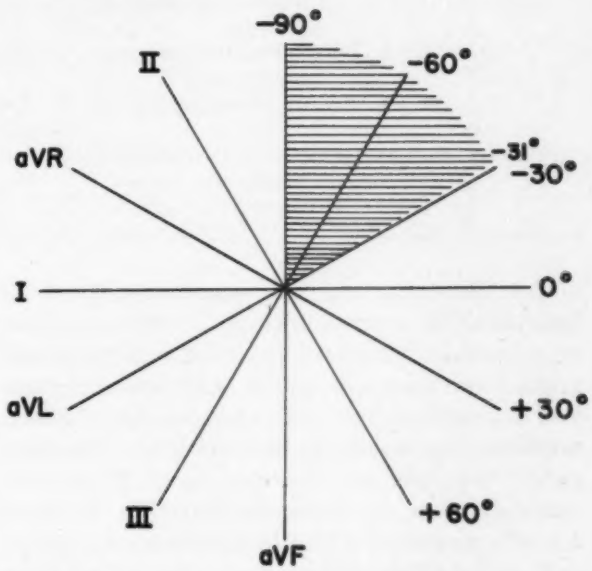

FIG. 2. Theoretical range of mean frontal P vector in coronary sinus rhythm (−31° to −90°).

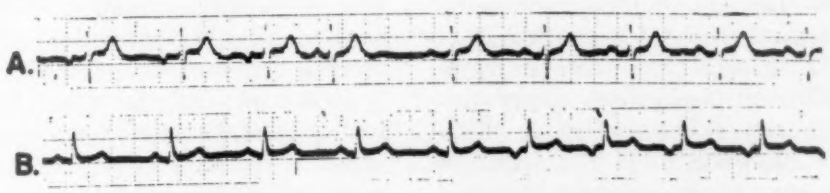

FIG. 3. Termination and initiation of coronary sinus rhythm. (Tracings were obtained on different dates from those recorded in Table 1.) A, Case 6; lead II. Coronary sinus rhythm (rate 74/min.) is terminated by a coronary sinus beat arriving 0.09 second early and is followed 0.56 second later by an atrial beat from a different focus. The ensuing pause is terminated by an apparent sinus pacemaker beginning with a slower beat and warming up to a rate of 79/min. The rates are similar during both mechanisms, but the faster sinus pacemaker assumes command. The P-R interval is slightly shorter during coronary sinus rhythm (0.16 vs. 0.17 second) but both are within normal limits. B, Case 4; lead aVF. Sinus mechanism (rate 73/min.) is abruptly replaced by a faster coronary sinus pacemaker (rate 88/min.). P-R interval decreases from 0.16 to 0.14 second but both are within normal limits.

TABLE I
Electrocardiographic Data

Clinical Data				Coronary Sinus Rhythm				
Case No.	Sex and Age	Diagnosis	B.P. (mm. Hg)	Rate (per min.)	Axis		Interval	
					P	QRS	P-R (sec.)	QRS (sec.)
1	M, 71	Emphysema; diabetes	145/100	84	−70°	+10°	0.15	0.07
2	F, 71	ASHD; emphysema; rheumatoid arthritis	139/100	58	−90°	+30°	0.14	0.06
3	M, 39	Psoriasis	120/80	67	−60°	+80°	0.14	0.08
4	F, 51	Rheumatoid arthritis, psoriasis	150/80	80	−90°	+60°	0.14	0.07
5	M, 73	Laennec's cirrhosis; ASHD; emphysema	114/80	68	−60°	0°	0.13	0.08
6	F, 74	ASHD; hypertension; diabetes	180/100	64	−60°	+70°	0.20	0.08
7	M, 53	Emphysema; chronic bronchitis	120/80	108	−60°	+90°	0.18	0.08
8	M, 54	Emphysema	100/60	96	−60°	−30°	0.16	0.10
9	F, 51	Emphysema; chronic bronchitis; hyperthyroidism	240/90	118	−90°	Indeterminate	0.14	0.08

onary sinus rhythm and sinus rhythm with normal P-R intervals (Fig. 3) also militate against this notion, defense of which would require the assumption that A-V nodal rhythm and forward A-V block occur not only simultaneously but also repetitively (Fig. 4). Furthermore, the uniform decrease in P-R interval during coronary sinus rhythm (Table I) is entirely consistent with a low atrial pacemaker.

Possible Mechanisms: It is likely that more than one mechanism may be responsible for tracings fulfilling the electrocardiographic criteria for coronary sinus rhythm. There is evidence for at least three: (1) In cases such as Langendorf's,[8] a proved pre-existing atrioventricular conduction impairment could continue during upper A-V nodal rhythm. This must be the rare exception. (2) The apparent specialized communications between the A-V node and the coronary sinus area[9,10] could account for preferential conduction of impulses from this region to the upper A-V node with or without shortening of the P-R interval (which, in any event, could remain within normal limits). Yet the locus of impulse initiation would be supranodal because of the similarity in rates during both sinoatrial and coronary sinus rhythms (Fig. 3A), since the inherent rate of impulse formation in the A-V node is ten or more beats per minute slower than in the sinus node. (3) Finally, pacemaker function could be usurped by either low atrial or upper nodal foci producing impulses at a faster rate than the sinus node (Fig. 3B) or by default to such foci by a sinus node which has altered its rate or mode of impulse formation. Figure 4 illustrates the default of atrial control to the coronary sinus pacemaker.

Assuming normal intra- and interatrial conduction, the fact that P wave inversions may be either symmetrical (Fig. 1) or asymmetrical (Fig. 4) further suggests multiple sites of origin of phenomena fulfilling the electrocardiographic criteria for coronary sinus rhythm. A more centrally located pacemaker (as, for example, in A-V nodal rhythm) would tend to produce symmetrical retrograde P waves because of more nearly equal spread of the wave front through both atria. An eccentrically situated focus would activate one atrium earlier. The fact that negative P waves in leads II and III may be produced by a left atrial pacemaker[7] would tend to support this concept. Pharmacologic induction of coronary sinus rhythm, previously noted, may be the result of either differential stimulation or inhibition of the sinus node and lower pacemakers by the particular agent employed.

TABLE 1
Electrocardiographic Data (*continued*)

Sinus Rhythm							
Rate (per min.)	Axis		Interval		Precordial P Inversion	Drugs	Other Arrythmias
	P	QRS	P-R	QRS			
...	...	...	...	...	V_1-V_6	Insulin	
56	+90°	+30°	0.17	0.06	V_1-V_6	Belladonna	Atrial fibrillation
...	...	...	...	...	None	Diphenylhydramine	
...	...	...	...	...	V_1-V_6		
68	+50°	−10°	0.17	0.08	V_3-V_6	Diuretics, KCl	Wandering pacemaker
58	+70°	+70°	0.21	0.08	None	Digitoxin, quinidine	Wandering pacemaker
78	+80°	+90°	0.20	0.08	None	Isoproterenol	Sinus arrhythmia
...	...	...	...	...	(Flat P V_1-V_6)	Proclorperazine	
118	+90°	Indeterminate	0.17	0.08	V_4-V_6	Methinazole	Frequent atrial ectopic beats

Course of Atrial Activation in the Horizontal Plane: Previous investigations of coronary sinus rhythm contain no reference to P wave orientation as recorded in precordial lead tracings. Five of our patients (Cases 1, 2, 4, 5 and 9) had clearly inverted P waves to position V_6. In three of these this was true of all precordial positions (Fig. 1); in one there was P inversion from lead V_3 to V_6 and in the fifth from lead V_4 to V_6. Of the remaining four patients one had isoelectric and three had upright P waves across the precordium. Thus, in some instances of coronary sinus rhythm net atrial activation apparently proceeds not only inferosuperiorly but also anteroposteriorly and from left to right, a pathway opposite in all planes to that of sinoatrially induced impulses. The fact that this is not true of all cases is further evidence of variability in the location of pacemakers capable of producing electrocardiograms which fulfill the criteria for this interpretation.

Coronary Sinus Rhythm vs. Coronary Nodal Rhythm: Similarity in terms inevitably results in confusion between coronary sinus rhythm and coronary nodal rhythm. Coronary nodal rhythm is characterized by upright P waves in leads I and II (theoretical mean frontal P vector between −29° and +89°) and a P-R interval which is clearly shortened (0.10 second or less). Yet coronary nodal rhythm is said to originate from "the region closest to the tail of the sinus node,"[11] a site hard by the ostium of the coronary sinus. The apparent result is a paradox in which two mechanisms having antithetical characteristics are thought to arise from very nearly the same locus. Either coronary nodal rhythm does not actually stem from here or conduction from this region to the rest of the atria must proceed by entirely different paths in the two rhythms. Apart from the differences in frontal P wave axis and atrioventricular conduction time, precordial tracings record upright P waves in coronary nodal rhythm. Furthermore, in our experience coronary nodal rhythm is a highly stable finding which is quite the opposite of coronary sinus rhythm. Eyring and Spodick[12] have presented evidence for the occurrence of accelerated A-V conduction (from either a normal sinoatrial pacemaker or an ectopic pacemaker) in coronary nodal rhythm, at least in those cases in which P axes are within the normal range.

SUMMARY

Coronary sinus rhythm is characterized by retrograde atrial activation with normal atrioventricular conduction time. It is always a transient phenomenon, is not associated with

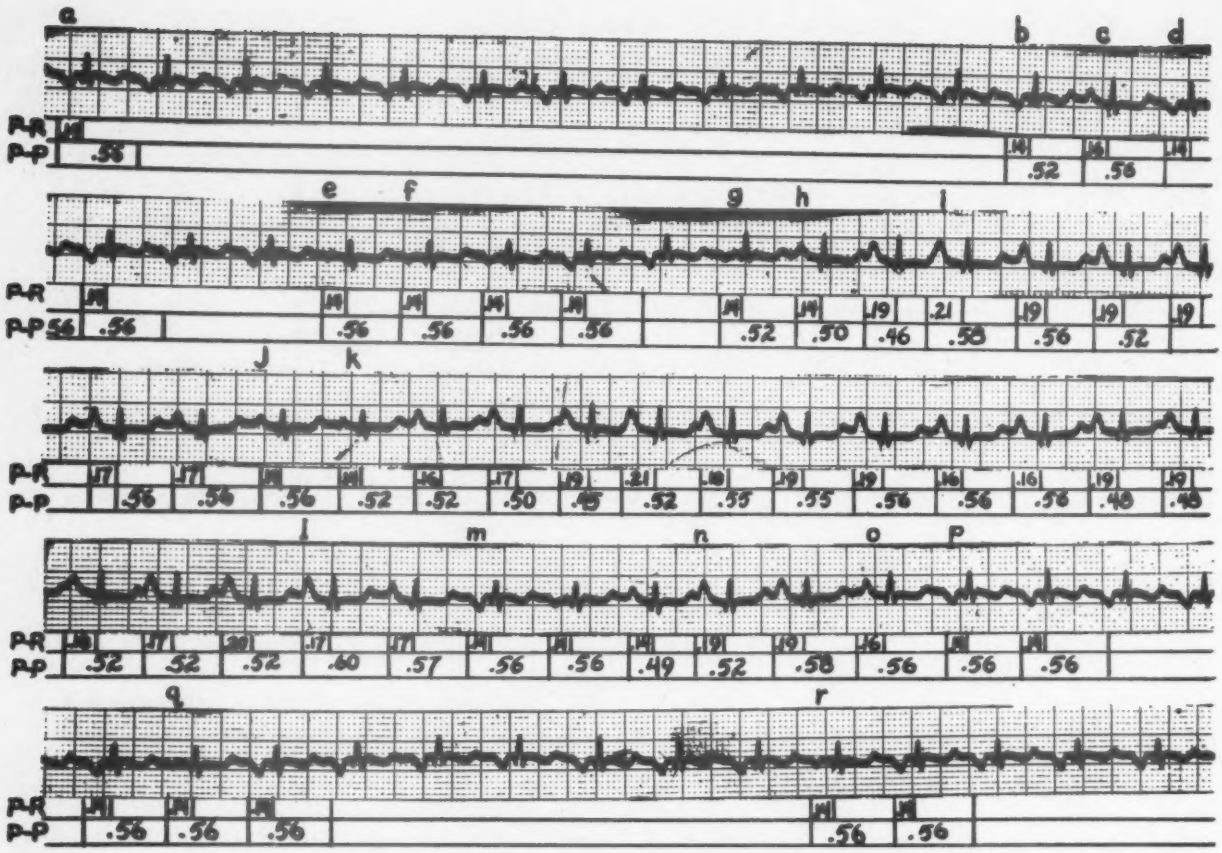

FIG. 4. Case 7; lead aVF. Default of control to the coronary sinus pacemaker by unstable higher atrial (and/or sinus) pacemakers. A continuous strip (40.8 seconds) showing coronary sinus rhythm as the dominant mechanism and more or less gradual transitions between the atrial and coronary sinus foci. The coronary sinus rhythm is interrupted only when higher pacemakers can achieve a faster rate. The latter are unstable and, in most instances, probably not of sinus origin as revealed by variations in P wave morphology, timing and P-R interval in successive beats. Transitional and/or fusion P waves are frequently seen. *Analysis: a and b*, coronary sinus rhythm (P-R = 0.14 second; P-P = 0.56 second; rate = 107/min.) is interrupted by a premature atrial beat at *c* (P-P = 0.52 second) but resumes at *d*. P waves of intermediate configuration (*e* and *f*) which are not premature (P-P = 0.56 second) do not cause interruption but another (*g*) is followed by a premature atrial beat (*h*) followed by yet another of different configuration. An even earlier beat (*i*, P-R = 0.46 second) is followed by an atrial rhythm from various foci at rates ranging from 133/min. to 100/min., without reversion to coronary sinus rhythm despite beats *j* and *k* which apparently originate in successively lower foci. The slowest beats (*l*) are followed by a coronary sinus beat (*m*) and a transitional beat after which the atrial pacemakers again take over (*n*). However, the run is terminated (*o*) by the more stable coronary sinus pacemaker (*p*) which maintains command. Transitional beats *q* and *r* at the identical rate cause no interruption.

specific pathologic states and can be induced in animals and normal human beings by simple pharmacologic measures. The behavior of the atrial complexes under experimental and clinical conditions is consistent with a low atrial (rather than upper nodal) focus of origin, at least in the overwhelming majority of instances. Analysis of P wave contour and spatial analysis of the direction of atrial activation suggest variability in the actual site of the pacemaker for this mechanism.

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Adams-Stokes Syndrome during Normal Sinus Rhythm and Transient Heart Block

III. The Paradoxical Effects of Carotid Sinus Digital Pressure and Deep Breathing on Patients with Adams-Stokes Seizures during Normal Sinus Rhythm and Transient Heart Block*

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IT is well known that patients with normal sinus rhythm who are sensitive to carotid sinus digital pressure may respond with a slowing of the heart rate due to vagal reflex or with a transient drop in arterial pressure resulting from systemic vasodilatation.[1,2] Cases have been recorded, however, in which carotid sinus pressure was followed by a transient acceleration of the heart rate instead of a slowing as was expected.[3]

Single and multiple extrasystoles[4,5] as well as tachycardias of the ventricles have been elicited with carotid sinus pressure in patients who were subject to such arrhythmias or after the administration of digitalis.[6,7] Moreover, changes from one type of accelerated heart action to sinus rhythm and *vice versa*[8] and all forms of atrial irregularities have likewise been noted to follow this maneuver.[9,10]

In studying the natural course of Adams-Stokes seizures in patients with normal sinus rhythm and transient heart block, it was found possible during certain phases of this illness to convert an A-V dissociation or a 2 : 1 heart block to sinus rhythm with carotid sinus digital pressure and deep breathing. The same measures caused standstill of the heart during complete heart block. It is the nature of these changes that we wish to discuss.

METHOD OF STUDY

Both left and right carotid sinus digital pressure and deep breathing were tried on ten patients who were subject to Adams-Stokes seizures during normal sinus rhythm or transient 2 : 1 heart block and complete heart block. These tests were performed prior and subsequent to ventricular asystole in the presence of sinus rhythm or during the various forms of heart block.

All maneuvers were performed with the patients in various postures such as lying flat, left and right reclining, sitting and standing.

Since vagal tone is known to be variable in the same person, every patient was subjected to repeated experiments within very short intervals as well as during the day and night, so as to note any diurnal or daily variations in these mechanisms.

Unless otherwise specified, no other drugs were used except isoproterenol (Isuprel®) sublingually in doses of 10 mg. The patients were kept in the electrocardiographic circuit throughout these tests and as many records were taken as was deemed essential to the study. Lead II only was used.

NATURAL COURSE OF ADAMS-STOKES SEIZURES DURING NORMAL SINUS RHYTHM AND TRANSIENT HEART BLOCK

The Adams-Stokes syndrome during normal sinus rhythm and transient heart block is very likely much more common than has been suspected hitherto. In most patients attacks may develop abruptly and in an unpredictable manner. Since the periods of ventricular asystole responsible for such attacks are of short duration, they may be missed entirely. Intervals of freedom from such seizures may be of long duration, and it may be only with prolonged observations that the cause of syncope can be discerned.

A characteristic feature of this syndrome is an unusual "labile" state of the cardiac mechanism both during the seizures and in between attacks, when the heart rhythm may vacillate

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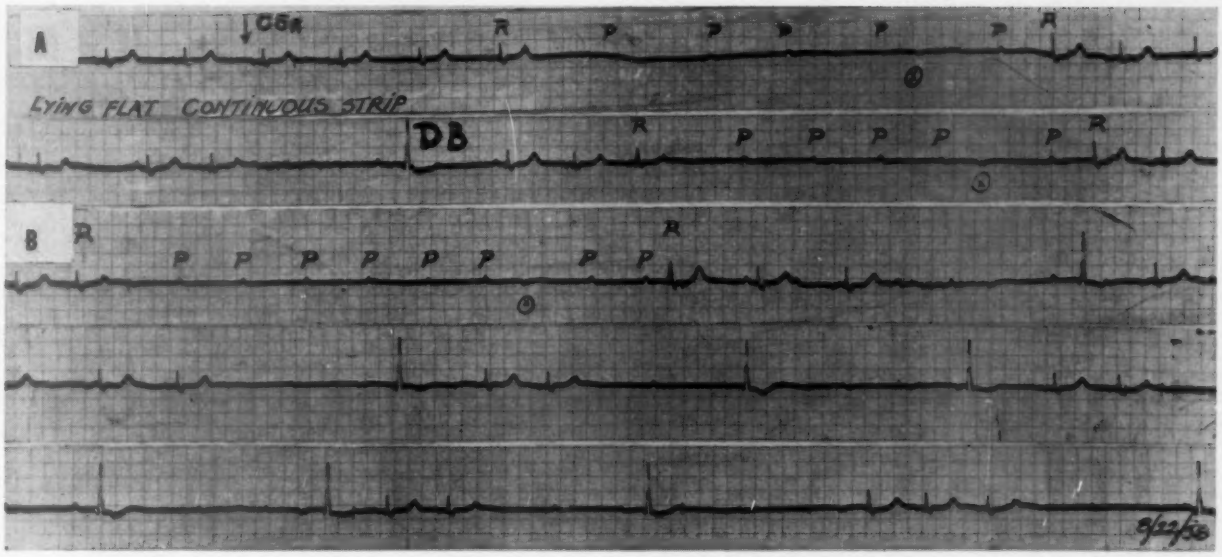

FIG. 1. A, carotid sinus digital pressure (CSR) and deep breathing (DB) resulted in ventricular asystole with a slow atrial rate. B, spontaneous ventricular asystole is associated with a progressive increase in the atrial rate.

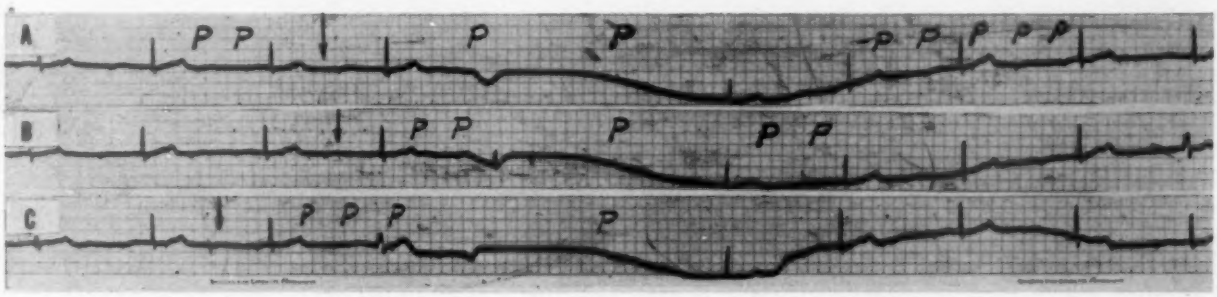

FIG. 2. The "labile" state. Digital pressure over the right carotid sinus (A and B) and over the left carotid sinus (C) yielded slowing of both the atria and ventricles during complete heart block.

from sinus rhythm to all forms of heart block even though asystole of the ventricles may be absent. These changes in rhythm have been attributed in part to the effects of the extrinsic nervous influences upon a diseased A-V node and its branches.[11] Others blame asystole of the ventricles on an acceleration of the atria in the preliminary phases that leads to stoppage of the heart.[12,13] It would appear that in some instances the A-V conduction mechanism is influenced by postural changes[14] and drugs so as to result in standstill of the ventricles.[15,16]

Some patients have been known to experience such seizures for as long as thirty-five years[17] with periods of freedom from attacks for eight years at a time.

Effects of Carotid Sinus Digital Pressure

during normal sinus rhythm

Only four of ten patients responded to the cardioinhibitory mechanism with digital pressure in the presence of sinus rhythm. In the others such maneuvers elicited no response even when ventricular asystole was interrupting the normal rhythm with increasing frequencies.

In our experiences with several hundred such tests in susceptible patients, no differences were noted in the response of the heart to digital pressure over the right carotid sinus as compared with the left. There is a general belief, based on meager evidence, that the sinus pacemaker in man is predominantly under the influence of the right carotid sinus or right vagus nerve, whereas the A-V pacemaker of the heart is influenced more by the left carotid sinus and left vagus nerve. When present, the carotid sinus cardioinhibitory responses were found to be the same on both sides in all postures.

In one type of response, complete asystole of the ventricles was accompanied by persistent atrial activity (Fig. 1A), while in another type, the whole heart stopped with only an occasional atrial beat or none at all (Fig. 2).

In the average patient with Adams-Stokes

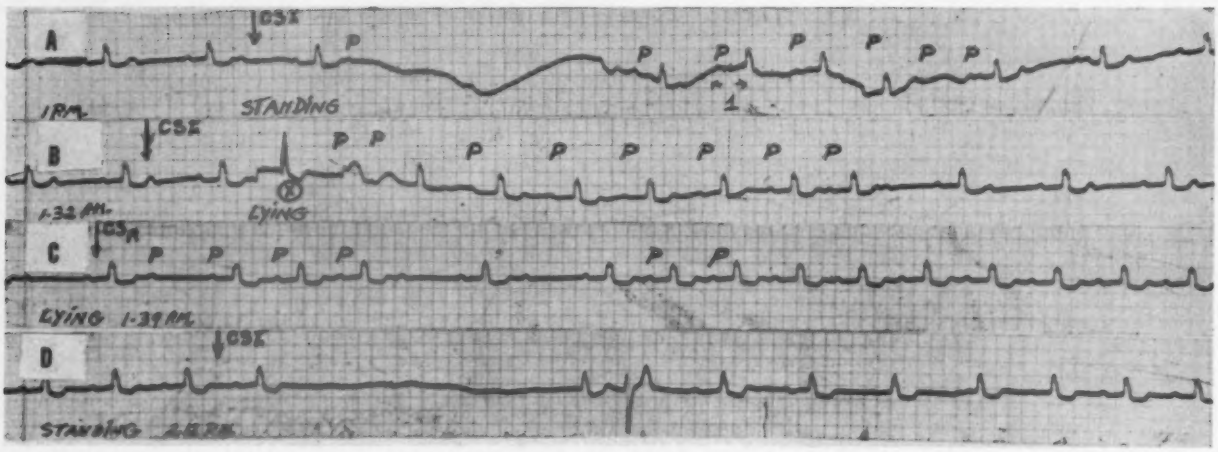

FIG. 3. A, left carotid sinus pressure (CSL) during 2:1 heart block caused standstill of the ventricles with two atrial beats present and temporary return to sinus rhythm. B, left carotid sinus pressure (CSL) converted a 2 : 1 heart block to sinus rhythm through the interposition of a well timed extrasystole (X). C, right carotid sinus pressure (CS) converted a 2:1 heart block to sinus rhythm. D, complete standstill of the heart after left carotid sinus pressure (CSL) during normal sinus rhythm.

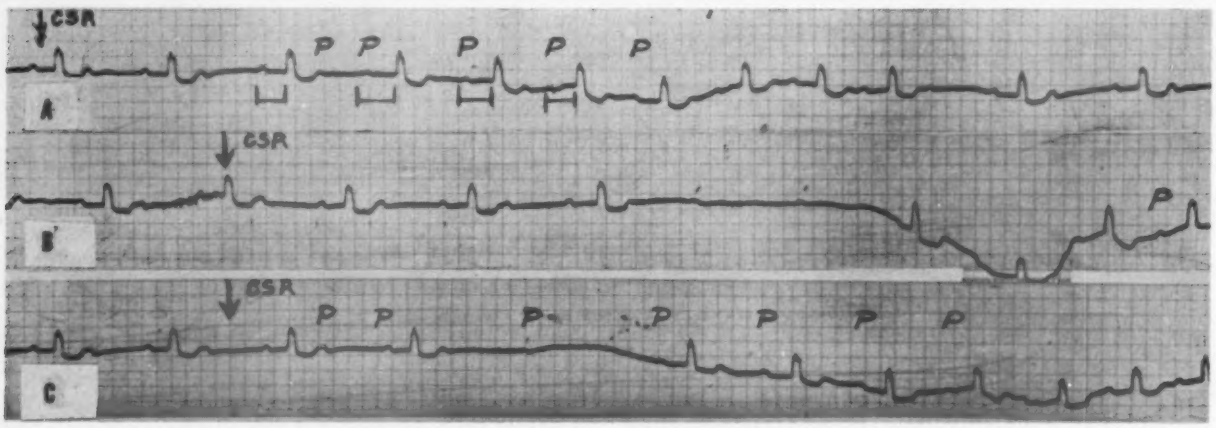

FIG. 4. A, conversion of 2:1 heart block to sinus rhythm without any change in the atrial rate. Note the variable increase in the P-R interval after right carotid sinus pressure (CSR) with return to sinus rhythm. There was a drop in blood pressure at this time. B and C, changes in the atrial rate with carotid sinus pressure (CSR) and return to sinus rhythm.

seizures, there is invariably a progressive acceleration of the atrial rate during the ventricular silences presumably due to an asphyxial state. Following carotid sinus digital pressure, even when allowances are made for the compensatory pauses that may follow an atrial premature beat, the atrial rate was slow at times and the rhythm irregular. The same type of atrial activity was found when deep breathing caused asystole of the ventricles (Fig. 1A). Such artificially induced periods could easily be distinguished by the activity of the atria from spontaneous attacks responsible for the ventricular asystole.

DURING COMPLETE HEART BLOCK

When complete heart block develops in patients with Adams-Stokes seizures during normal sinus rhythm, it may appear after repeated syncopal seizures and may last only temporarily from a few minutes to as long as a few weeks and then disappear with a return of the sinus rhythm. It may also appear as an established phenomenon and remain so for the rest of the patient's life.

At certain stages in the development of the complete heart block with regular atrial and ventricular rhythms, the ventricular complexes may remain the same size, shape and form as the basic ventricular complexes that were present during sinus rhythm. Sooner or later, the A-V pacemaker shifts and the ventricular complexes gradually change their form and become aberrant although their rate remains the same. In this "labile" phase, when the ventricular complexes are still of the supra-

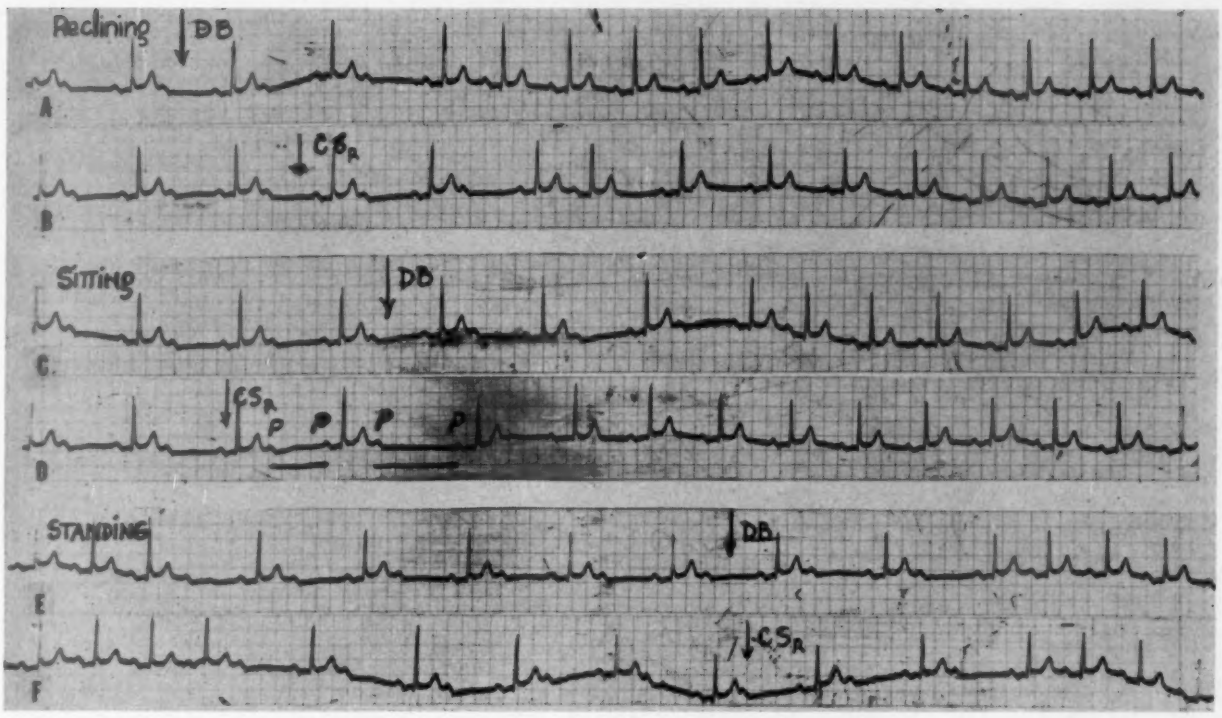

FIG. 5. Alternate deep breathing (DB) and carotid sinus pressure (CSR) convert a 2:1 heart block to sinus rhythm. Note the progressive slowing of the atrial rate in D prior to appearance of sinus rhythm.

ventricular type and varying, both the atria and ventricles become unusually sensitive to the carotid cardioinhibitory mechanism. In three of the ten patients studied both left and right carotid sinus digital pressure caused a transitory complete stoppage of both the atria and ventricles (Figs. 2A, B and C).

This phenomenon, in addition to being an index of the labile state of the heart, offers an explanation for the augmented vagal inhibitory action of digitalis glycosides in such patients during complete heart block.[18]

DURING 2:1 HEART BLOCK

If sufficient observations are made on these patients, it will be noted that at some time or other, they all reveal a transitory phase of 2:1 heart block. A temporary return to normal sinus rhythm followed carotid sinus pressure in five patients who showed this mechanism (Figs. 3A, B, C and 4). Several possibilities exist as explanations for the nature of these events:

1. It is well known from experimental observations in the higher mammalian heart that faradization of the ventricles may cause a complete but temporary cessation of both atrial and ventricular activity. Following stoppage of the whole heart during which time both the sinus and A-V nodes may renew and build up impulse formation, the heart may begin to beat faster than at any time previously. It is then that sinus rhythm may reappear. Such changes have been observed clinically in the post-standstill periods following transient ventricular fibrillation.[19] It seems plausible that a similar mechanism may also play a part in the temporary restoration of the sinus rhythm after stoppage of the heart as a result of digital pressure over the carotid sinus, at least in this type of record.

2. A secondary fall in blood pressure after carotid sinus pressure in the course of 2:1 heart block even though of short duration may result in a sympathetic discharge rather than a vagal one. Therefore, the possibility that epinephrine liberated at such times may enhance the heart rate and facilitate improvement in conduction so as to bring about a sinus rhythm is also to be considered (Fig. 4A).

3. Engelman[20] pointed out that a primary slowing of the impulse formation in the sinus node resulted in a secondary improvement in A-V conduction. One result of carotid sinus stimulation may be a slowing of the sinus rate (Fig. 5). This mechanism has been found to be the most common one associated with "deblocking" of the heart during the "labile" state. Given the fortuitous periods of atrial

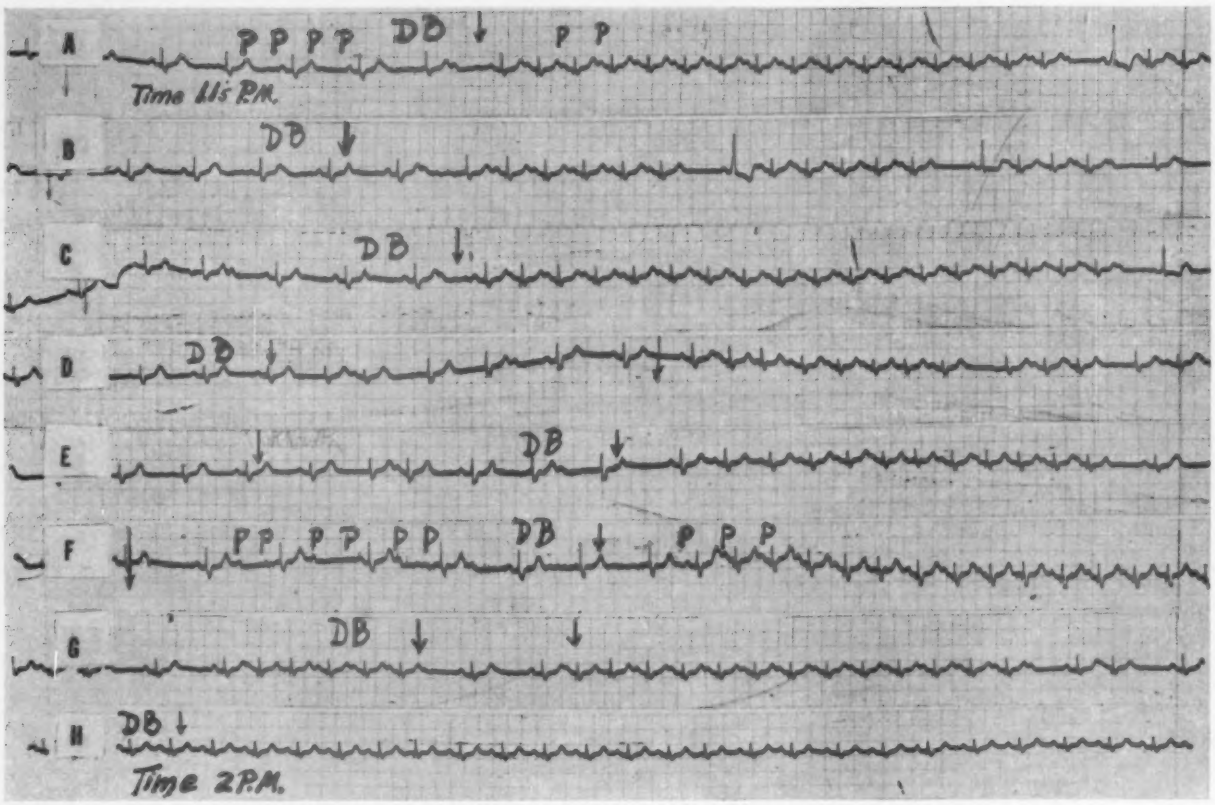

FIG. 6. Progressive increase of sinus beats after deep breathing following the use of isoproterenol.

slowing with improvement in A-V conduction, it is likely that normal sinus rhythm may supervene.

4. The appearance of ectopic impulse formation in the ventricles following carotid sinus pressure in man is not uncommon. Mines[21] has called attention to the fact that a transition from "half" to "whole" rhythm during heart block in turtles may be brought about by the interposition of an extra stimulus to the heart at the proper time. This extrasystole will have a refractory phase shorter than that of the preceding beats and probably so short that the next stimulus will fall outside it. Once started, this new rhythm may continue uninterrupted. "Deblocking" of the heart can therefore result from premature beats alone in addition to the fortuitous circumstances at the time of their appearance (Fig. 5B).

PARADOXICAL EFFECTS OF BREATHING

Experimental observations have revealed that any abnormal inflation of the lungs invariably brought about a conspicuous retardation or even arrest of the heart rate.[22] In human subjects deep breathing has been found to result in cardiac slowing not only during sinus rhythm[23,24] but also in an occasional patient with heart block.[25] These inhibitory actions upon the heart have been attributed to vagal reflexes originating in visceral and parietal pleura or in the tissues underlying and arising in part from (1) the mechanical changes in the lung incident to the act of breathing; (2) the dual action of the respiratory center on the vagus nucleus; and (3) possible periodic variations in the components of the blood such as hypoxia and acid-base electrolyte imbalance.

Deep breathing following the use of epinephrine has resulted in the development of premature beats of the ventricles and infrequently in the appearance of atrial fibrillation. In a few patients deep breathing has resulted in the appearance of Adams-Stokes seizures in patients with normal sinus rhythm and transient heart block.

With the patients in different postures, deep breathing was found to convert a 2:1 heart block to normal sinus rhythm in five patients in whom carotid sinus digital pressure yielded the same changes (Fig. 5). The most common denominator responsible for these changes at such times was a transitory slowing of the atrial rate with improvement in A-V conduction

immediately before the conversion of the 2:1 heart block to normal rhythm.

This method of deblocking with deep breathing was present not only during the "labile" periods when these patients were subject to Adams-Stokes seizures but at other times when they were free from attacks. In one patient such a state lasted for almost a year in the absence of any periods of ventricular asystole, and the rhythm vacillated between 2:1 heart block and normal sinus rhythm without the patient being conscious of his heart at any time.

During certain phases of this illness, deep breathing resulted in asystole of the ventricles as readily as with carotid sinus digital pressure. Compare carotid sinus pressure with deep breathing in Figure 1.

Isoproterenol was found to sensitize these mechanisms early after its use in such patients. It facilitated deblocking until the sinus rate was sufficiently stimulated to accelerate the heart and overcome the reflex vagal effects (Fig. 6).

Summary and Conclusions

A study was made of the effects of carotid sinus digital pressure and deep breathing on ten patients who were subject to Adams-Stokes seizures during normal sinus rhythm and transient heart block.

In three of the ten patients these maneuvers resulted in a temporary slowing of the heart with transitory development of various forms of heart block at a time when their rhythm was normal.

During transitory complete heart block, an unusual sensitivity to carotid sinus digital pressure developed in three patients which resulted in stoppage of both the atria and ventricles.

When the rhythm in five patients was that of a 2:1 heart block, the same maneuvers performed alternately resulted in the transitory appearance of normal rhythm.

If allowances are made for the daily and diurnal variations in the carotid sinus reflexes, both right and left carotid sinus digital pressure were found to yield the same results.

Isoproterenol was found to sensitize the carotid sinus and deep breathing reflexes so that blocking and deblocking in such patients may be present for long periods in the absence of Adams-Stokes seizures.

The paradoxical development of sinus rhythm following carotid sinus pressure and deep breathing in such patients may be attributed in part to (1) an improvement in A-V conduction through a slowing of the atrial rate; (2) the liberation of epinephrine following compensatory vasoconstriction after a transient drop in blood pressure due to carotid sinus reflexes; (3) a change in the pacemaker of the heart as a result of the appearance of a well timed extrasystole when a slower rhythm can be converted to a more rapid one; and finally (4) to the building up of impulse formation with escape of the sinus pacemaker during induced standstill of the whole heart.

The unpredictable alterations in the cardiac mechanisms resulting from such changes are in part responsible for the difficulties encountered in the treatment and prevention of ventricular asystole in such patients.

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Experimental Studies

Study of the Transmembrane Action Potential, Electrogram, Electrocardiogram and Vectorcardiogram of Rats with Left Ventricular Hypertrophy*

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ALTHOUGH clinical and electrocardiographic changes associated with left ventricular hypertrophy have long been recognized,[1-8] the electrophysiologic mechanisms underlying such changes have not been clarified. Accordingly, various parameters of electrical activity were studied in hypertensive rats with left ventricular hypertrophy and compared with similar studies in control animals.

METHODS

A series of Long-Evans male rats (age six weeks) was subjected to a one stage uninephrectomy and application of a figure-of-eight ligature around the contralateral kidney.[9,10] Five to eight months later ten hypertensive rats were studied, whose blood pressures had been persistently elevated and whose final systolic blood pressures ranged from 130 to 180 mm. Hg, as determined by the microphonic manometer.[11] The rats were then anesthetized with intraperitoneal Nembutal® (0.06 ml./kg.), and bipolar electrocardiographic tracings were recorded successively from three axes of the chest (Fig. 1). A superoinferior (S-I) axis was formed by electrodes in the right posterior axillary line at the level of the front paw (−) and 2.5 inches caudal (+). A second axis, posteroanterior (P-A), was formed by using the latter electrode (−) with a second electrode (+) in the right anterior axillary line at the same body level. A third axis, right to left (R-L), was formed by using the same negative electrode as in the P-A axis with an electrode (+) in the left posterior axillary line at the same body level. Amplification of the recorded tracings was provided by a Tektronix 122 amplifier, and the tracings were visualized on a Hewitt-Packard 130A oscilloscope and photographically recorded with a DuMont 302 Polaroid camera.

Vectorcardiograms were obtained by simultaneously recording voltages from two of the three axes on the horizontal and vertical deflecting plates of a Hewitt-Packard 130A oscilloscope after amplification with Tektronix 122 preamplifiers. The frontal, sagittal and horizontal planes were formed by presenting voltages to the vertical and horizontal deflecting plates from the S-I and R-L axes, the S-I and P-A axes, and the P-A and R-L axes, respectively.

Surface and Transmembrane Myocardial Potentials: After recording the electrocardiograms and vectorcardiograms, a tracheotomy was performed and the trachea was connected by a polyethylene tube to a respirator. The pericardium then was excised through a thoracotomy incision and the myocardium exposed. Transmembrane and surface myocardial potentials then were obtained by means of a glass microelectrode which was filled with 3 M potassium chloride and connected by a tungsten wire to the input of a Grass P-7 microelectrode probe mounted on a micromanipulator and preamplifier.[12] The indifferent electrode consisted of an Ag-AgCl wire inserted beneath the diaphragm. With the microelectrode in a single cell, characteristic baseline drop (negative resting potential) and monophasic transmembrane action potentials were obtained;[12-15] and when the electrode rested on the surface of the heart, polyphasic electrograms were obtained. Recordings of transmembrane action potentials and surface electrograms were made at nine different

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TABLE 1
Comparison of Electrocardiograms in Control and Experimental Animals

Recording Axis	Type of Rat	ECG Wave	Average Amplitude (mv.)
Superoinferior	Control	P	86 ± 9* (45–143)†
	Experimental		92 ± 5 (71–134)
	Control	Q	3 ± 2 (0–8)
	Experimental		1 ± 4 (0–27)
	Control	R	507 ± 31 (375–625)
	Experimental		640 ± 24 (536–732) P < 0.01
	Control	S	43 ± 18 (0–179)
	Experimental		25 ± 9 (0–89)
	Control	T	137 ± 13 (80–196)
	Experimental		128 ± 10 (89–179)
Posteroanterior	Control	P	0
	Experimental		3 ± 2 (0–8)
	Control	Q	0
	Experimental		0
	Control	R	46 ± 12 (0–89)
	Experimental		73 ± 15 (0–142)
	Control	S	3 (0–36)
	Experimental		12 ± 8 (0–89)
	Control	T	5 ± 8 (0–27)
	Experimental		10 ± 5 (0–36)
Right-left	Control	P	3 (0–27)
	Experimental		5 ± 3 (0–27)
	Control	Q	0
	Experimental		1 (0–8)
	Control	R	188 ± 15 (125–294) P <0.05
	Experimental		137 ± 15 (53–214)
	Control	S	12 ± 6 (0–54)
	Experimental		37 ± 10 (0–116)
	Control	T	5 ± 24 (0–36)
	Experimental		6 ± 5 (−18–27)

* Standard error of mean.
† Range of values.

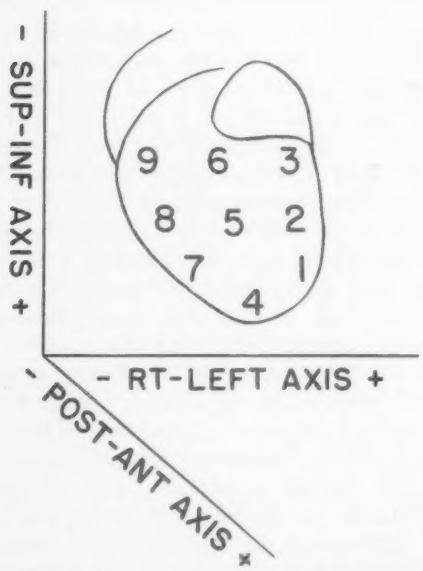

FIG. 1. The location of the axes used for recording the electrocardiograms and vectorcardiograms and the areas of the heart from which transmembrane potentials and electrograms were recorded.

sites of the myocardium (Fig. 1). Subsequently, the hearts were removed, blotted dry and weighed. For control purposes, similar studies also were done in ten normal rats of similar body weights and whose final systolic blood pressures ranged from 95 to 130 mm. Hg.

RESULTS

The occurrence of left ventricular hypertrophy in the hypertensive rats was verified by the finding, as shown in Figure 2, that the dry heart weights of the experimental rats were significantly greater than expected, when related to their body weights.[16]

Electrocardiograms: Bipolar electrocardiograms were obtained in three axes (Table 1). In the superoinferior axis, the R wave amplitude averaged 640 mv. (range: 536–732), significantly greater ($p < 0.01$) than the average amplitude of 507 mv. (range: 375–625) in the control rats. In the right-left axis the R wave amplitude averaged 137 mv. (range:

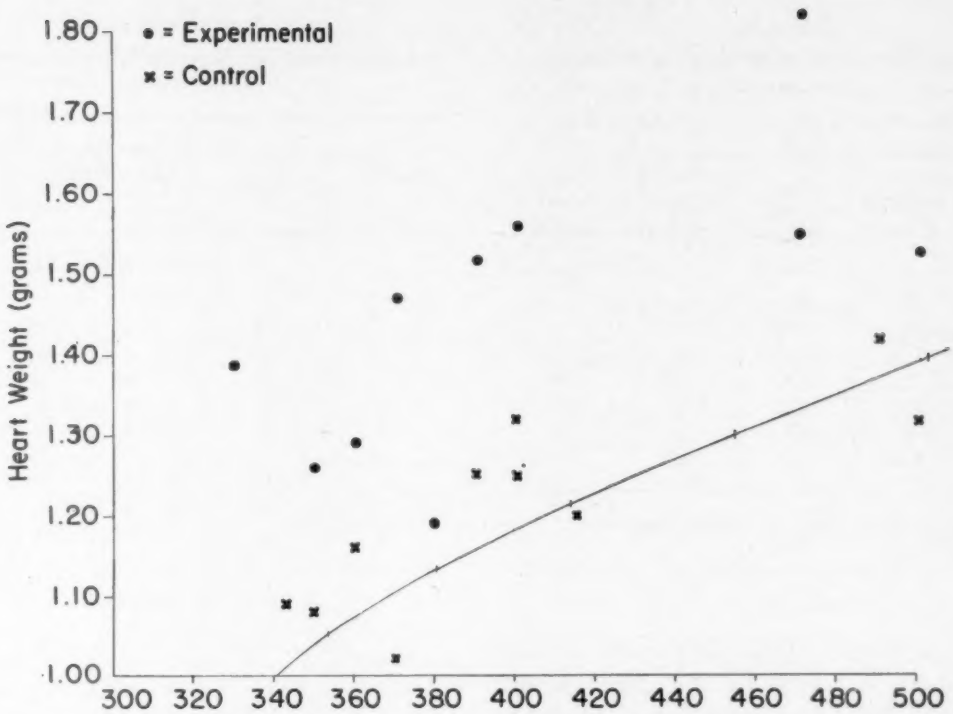

FIG. 2. The relationship of heart and body weights (gm.) of the experimental and control rats. (The line curve depicts the predicted heart-body weight relationship of normal rats.[16])

53–214), again significantly differing ($p < 0.05$) from the average of 188 mv. (range: 125–294) in the control rats. In the posteroanterior axis the R wave amplitudes were not significantly different. Slight differences in the amplitudes of the remaining waves of the electrocardiograms were not statistically significant.

Vectorcardiograms: In Figure 3 it can be seen that the mean QRS vectors in the frontal plane were of significantly greater magnitude and located more inferiorly and to the right in the experimental rats' tracings than in the controls. On the other hand, there were no significant differences in the degree of posteroanterior displacement of the vectors recorded in the two series of rats. The most frequently observed vectorcardiographic pattern occurred in five experimental and four control rats (Table II) and consisted of a counterclockwise inscription in the frontal plane, clockwise in the sagittal plane and counterclockwise in the horizontal plane. The remaining five experimental rats exhibited a pattern consisting of clockwise inscription in the frontal plane, "edge," clockwise or counterclockwise in the sagittal plane and clockwise or counterclockwise in the horizontal plane. In contrast, none of the control rats exhibited a clockwise inscription

FIG. 3. Relationships of mean QRS vectors in experimental and control rats in the frontal plane.

TABLE II
Direction of Inscription of the Vectorcardiograms*

Vector Pattern			No. of Rats	
Frontal Plane	Sagittal Plane	Horizontal Plane	Control	Experimental
E	E	E	4	
CC	E	CC	2	
CC	C	CC	4	5
C	E	CC		2
C	C	CC		1
C	C	C		1
C	CC	C		1

* C = clockwise; CC = counterclockwise; E = "edge" pattern.

TABLE III
Average Amplitude of the Electrograms in Control and Experimental Rats

Area*	No. of Rats	Average Amplitude of the Surface Potential R + S Waves (mv.)
	Control Rats	
9	8	36 ± 3.6† (22–52)‡
8	9	43 ± 1.6 (36–50)
7	10	44 ± 3.3 (27–62)
6	10	44 ± 3.8 (26–58)
5	10	54 ± 2.8 (42–68)
4	10	50 ± 3.8 (33–70)
3	10	42 ± 3.5 (22–60)
2	10	46 ± 2.0 (34–54)
1	10	48 ± 2.4 (38–58)
	Experimental Rats	
9	6	38 ± 5.6 (18–60)
8	9	43 ± 2.3 (32–52)
7	9	43 ± 3.5 (26–62)
6	9	54 ± 4.9 (30–76)
5	9	56 ± 3.5 (40–66)
4	8	49 ± 5.6 (22–70)
3	7	41 ± 3.5 (28–56)
2	8	46 ± 4.3 (28–70)
1	8	50 ± 3.2 (36–60)

* Locations of areas are seen in Figure 1.
† Standard error of the mean.
‡ Range of values.

in the frontal plane. Thus the control animals exhibited a counterclockwise or "edge" pattern in the frontal plane, and "edge" or clockwise in the sagittal plane and a counterclockwise or "edge" pattern in the horizontal plane.

Electrograms: Electrograms were recorded in the experimental and control rats from the pericardial surface of the myocardium at each of the nine sites indicated in Figure 1. As can be noted in Table III, the amplitudes of the combined R + S waves at each site showed no significant differences in the control and experimental rats. Furthermore, as shown in Table IV, no significant differences between the R waves and S waves were noted in the electrograms of the two groups of rats recorded from the same respective sites, except at the apical area (area 4, Fig. 1). In the latter instance the R wave obtained from the experimental rats averaged 21 mv. (range: 18–28), significantly smaller ($p < 0.01$) than the average of 33 mv. (range: 18–43) in the control rats.

Transmembrane Action Potentials: As shown in Table V, no significant differences were noted in the transmembrane action potentials recorded from the same respective nine areas in the control and experimental groups of rats.

COMMENTS

Sodi-Pallares[3] has considered the factors of increased muscle mass, altered anatomic position and delayed intraventricular conduction in the genesis of the QRS complex changes observed in the electrocardiograms of subjects with left ventricular hypertrophy. The present data suggest that the factor of increased muscle mass is of particular importance in this regard. Thus, larger R waves and increased mean vector magnitudes were respectively observed in the electrocardiograms and vectorcardiograms obtained from the rats with left ventricular hypertrophy, findings comparable to the increased QRS voltages in tracings obtained from human subjects with left ventricular hypertrophy. However, when the heart weights *per se* were plotted aginst the R wave voltages observed in the S-I axis (see Fig. 4), the coefficient of correlation ($r = 0.234$) indicated that the relationship was not statistically significant. On the other hand, when the same R wave voltages were plotted against the difference in heart weight from the predicted heart weight (see Fig. 5), a significant correlation was obtained ($r = 0.748$). Thus, it was observed that a proportionate increase of R wave voltage had actually occurred for each increment of

TABLE IV

Average Amplitude of the Components of the Electrogram

Area	No. of Rats	Average R Wave Amplitude (mv.) / Average S Wave Amplitude (mv.)
		Control
9	8	25 ± 3.7* (10–42)†
		11 ± 2.1 (4–20)
8	9	20 ± 4.4 (4–38)
		23 ± 3.3 (8–32)
7	10	23 ± 2.9 (8–32)
		21 ± 3.1 (6–36)
6	10	33 ± 3.3 (14–46)
		11 ± 1.5 (4–20)
5	10	36 ± 3.6 (20–54)
		19 ± 2.1 (10–28)
4	10	33 ± 2.2 (18–43)‡
		17 ± 3.7 (1–32)
3	10	30 ± 4.8 (10–50)
		13 ± 2.5 (6–29)
2	10	27 ± 3.6 (8–41)
		19 ± 3.3 (8–40)
1	10	29 ± 3.3 (14–48)
		19 ± 2.3 (8–28)
		Experimental
9	6	19 ± 3.5 (4–24)
		22 ± 5.5 (6–40)
8	9	22 ± 3.5 (9–40)
		21 ± 2.7 (10–36)
7	9	24 ± 1.8 (16–32)
		20 ± 3.9 (4–36)
6	9	40 ± 5.2 (14–60)
		14 ± 3.7 (4–42)
5	9	29 ± 5.7 (10–56)
		27 ± 4.7 (8–52)
4	8	21 ± 1.7 (18–28)‡
		28 ± 5.1 (4–44)
3	7	25 ± 4.8 (8–48)
		16 ± 3.1 (8–26)
2	8	25 ± 3.2 (12–42)
		22 ± 5.2 (8–48)
1	8	29 ± 3.9 (16–44)
		21 ± 4.7 (2–36)

* Standard error of the mean.
† Range of values.
‡ $P < 0.01$.

TABLE V

Transmembrane Action Potential in Control and Experimental Rats

Area	No. of Recordings*	Average Transmembrane Potential (mv.)
		Control
9	4	92 ± 2.2† (86–96)‡
8	8	84 ± 2.4 (70–90)
7	12	88 ± 1.1 (90–92)
6	16	93 ± 1.7 (80–102)
5	35	89 ± 1.1 (70–100)
4	38	92 ± 1.0 (72–104)
3	12	90 ± .7 (80–100)
2	19	89 ± 1.2 (76–98)
1	19	89 ± 1.1 (80–100)
		Experimental
9	2	88 ± 6 (82–94)
8	5	88 ± 2.4 (80–94)
7	10	89 ± 2.0 (80–100)
6	11	89 ± 2.2 (70–96)
5	39	91 ± 1.1 (70–100)
4	26	89 ± 1.3 (76–100)
3	11	90 ± 1.8 (76–98)
2	25	91 ± 1.3 (80–104)
1	16	87 ± 2.0 (68–101)

* Each recording consists of a separate introduction of the microelectrode into the myocardial fiber.
† Standard error of the mean.
‡ Range of values.

heart weight in excess of that predicted for a rat of the respective body weight. Indeed, if a line of regression were to be drawn ($y = 495.1 +$ 479.3 x), it appeared that the R wave voltage in the S-I axis had increased by approximately 50 mv. for each 0.10 gm. increase in heart weight, within the limits of the values recorded. The data therefore strongly suggest that the augmented voltages recorded during depolarization of the hypertrophied heart are engendered in major part by the *additional* tissue mass through which the advancing wave front must pass, particularly since this occurs unopposed by forces generated during the earlier activation of the normal septum and right ventricle.

This conclusion, of course, assumes that the velocity of conduction is not significantly delayed in the hypertrophied muscle mass, a possible contributing cause of the augmented QRS amplitudes which was not assessed by the present data. On the other hand, the finding herein of similar transmembrane action potentials in hypertrophied and normal hearts

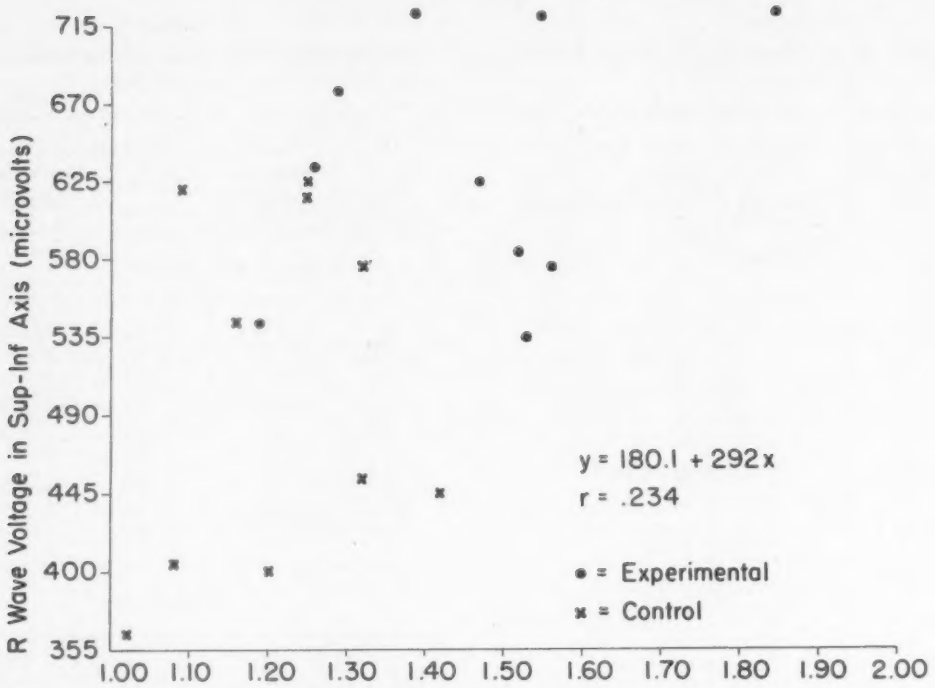

FIG. 4. Graph showing lack of correlation between heart weights (gm.) and R wave voltages in the electrocardiograms (S-I axis) of experimental and control rats.

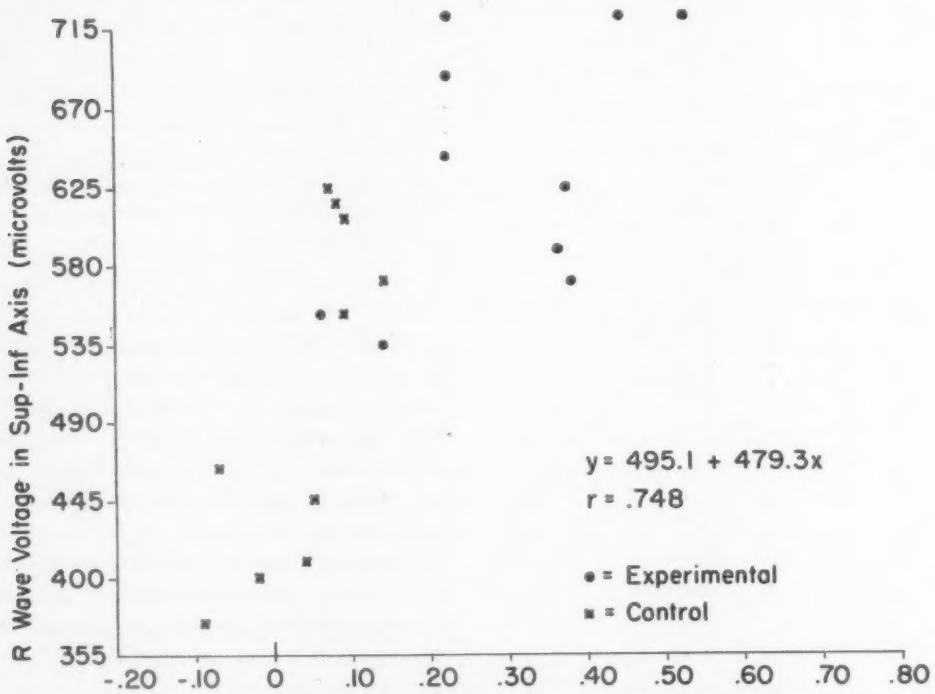

FIG. 5. Graph showing significant relationship of the R wave voltage in the S-I axis and the difference in actual heart weight from that predicted for the normal rat of the same body weight (gm.).

indicates that the augmented QRS amplitudes recorded from the hypertrophied hearts are not ascribable to any increase in the magnitude of the single cell generator.

SUMMARY

Transmembrane action potentials, electrograms (surface potentials), electrocardiograms (bipolar potentials) and vectorcardiograms were

recorded in a series of renal hypertensive and normal control rats. The vector- and electrocardiograms in hypertensive rats with left ventricular hypertrophy exhibited mean QRS vectors and R waves in the superoinferior (S-I) axis that were of significantly larger amplitudes than recorded in the normal rats. Although no significant relationship was found between R wave voltages and heart weights in the S-I axis tracings, a significant linear relationship was found between the difference of the heart weight from the predicted heart weight of the control rats and the S-I axis R wave voltage. No differences were noted in the transmembrane action potentials recorded in the two groups of rats.

On the basis of the observed findings it is concluded that the augmented QRS voltages observed in the electrocardiogram obtained from the hypertrophied heart may be engendered primarily by the increased muscle mass through which the advancing wave front must pass during its depolarization. No evidence was found of any increase in the magnitude of the single cell voltage generated by the hypertrophied heart.

Acknowledgment

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Hemodynamic Effects of Balloon Obstruction of the Abdominal Aorta and Superior Vena Caval-Distal Aortic Shunting in Dogs with Myocardial Infarction and Shock*

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IN PATIENTS with myocardial infarction with shock who do not respond to vasopressor agents, extracorporeal circulatory support might prove useful in temporarily maintaining the circulation to vital areas. The major therapeutic objective is to produce a sustained increase in central aortic pressure and hence an increase in coronary and cerebral perfusion. An increase of aortic pressure appears to increase survival rates in this condition.[1,2] There is strong evidence that arterial pressure is a major determinant of coronary flow.[3–7] Experimentally, improvement in coronary flow increases the blood supply to ischemic as well as normal areas of the myocardium[8] and improves the function of both right[9] and left[10] ventricles. Improvement in cerebral perfusion which is attained when the blood pressure is normalized is probably also beneficial. While achieving a rise in central aortic pressure, an ideal method of extracorporeal circulatory support should not be accompanied by a damaging increase in left ventricular work.

Previously reported studies[11] of prolonged, extracorporeal circulatory support in dogs with a closed chest have shown that relatively large flows (averaging 60 cc./kg./minute) may be obtained with simple peripheral cannulations and that these can be maintained for several hours. When a cardiac output was present, however, even large volumes of blood shunted from the venae cavae into the abdominal aorta failed to produce a rise in central aortic pressure in either normal animals or in those with hypotension following coronary embolization.[11] To increase coronary perfusion pressure by means of extracorporeal circulation in these animals, it was necessary to increase systemic vascular resistance. This was accomplished in the dog with a closed chest by inflating a balloon catheter introduced via a femoral artery into the abdominal aorta, supplying the distal aorta below the obstruction with blood pumped from the superior vena cava. This report will assess the hemodynamic effects of this method in animals with myocardial infarction accompanied by shock.

METHODS

Pentobarbital (30 mg./kg.) was injected intravenously for anesthesia. Pressures were recorded through Statham strain gauges and cardiac outputs were determined by the dye dilution method with sampling of Evans blue from a carotid artery, as previously outlined.[11] Twelve dogs were studied for periods of two to four hours. In ten experiments the chest was kept closed. In two the chest was opened and a peripheral branch of the left anterior descending coronary artery was cannulated with a polyethylene catheter. During the control period and at thirty minute intervals throughout the experiment duplicate determinations of the rate of flow

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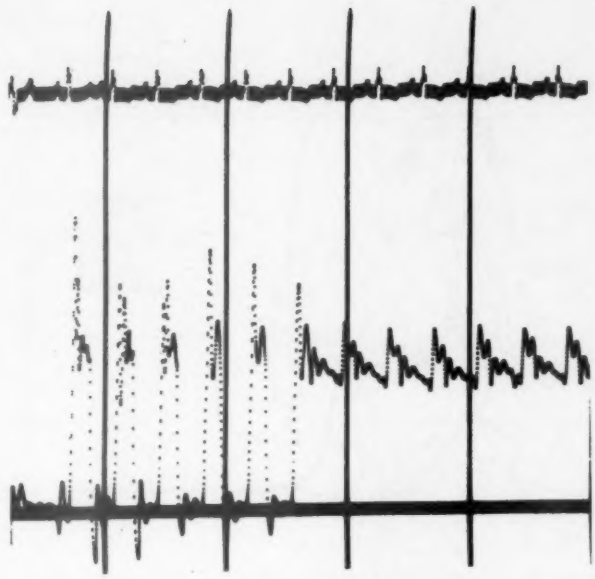

FIG. 1. Pressures obtained during positioning of the catheter through which plastic spheres were injected into the coronary circulation. A thin-walled Lehman aortographic catheter was passed via a femoral artery into the left ventricle and was then withdrawn through the aortic valve until an aortic tracing was obtained. Plastic spheres suspended in 15 per cent acacia in saline were injected under pressure during transient cardiac arrest produced by 0.4 mg./kg. acetylcholine injected rapidly intravenously.

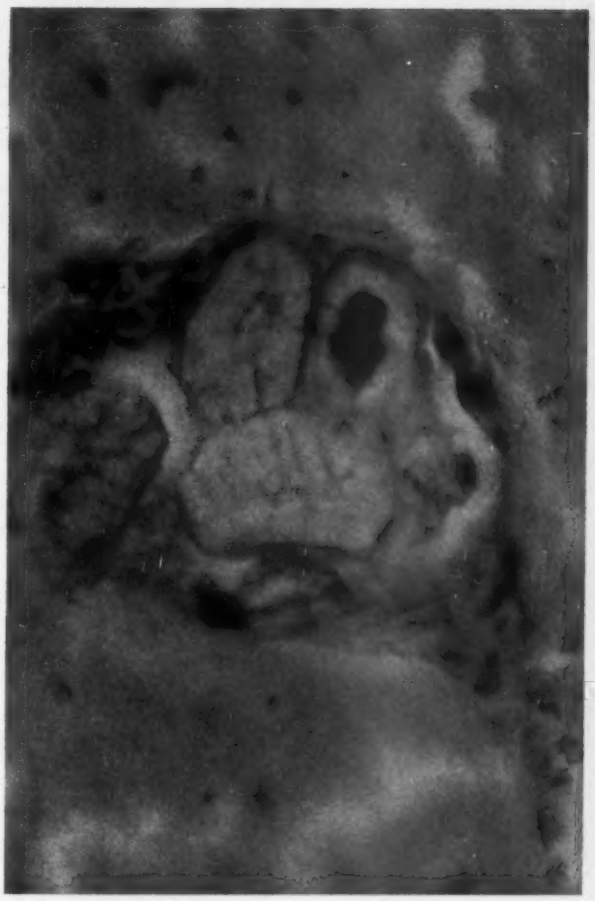

FIG. 2. Photomicrograph of peripheral coronary vessel occluded by plastic spheres; hematoxylin and eosin ×400.

from this branch were measured for thirty seconds by drainage into a graduate held at the level of the left ventricle. Left ventricular pulse pressures were recorded periodically through No. 20 gauge needles inserted directly into the ventricular cavity in two dogs with open chests and percutaneously in 3 animals with closed chests. Right atrial pressures were recorded via standard Cournand catheters inserted via a femoral vein.

Myocardial infarction with shock was produced by a modification[11] of the method of Agress.[12] Two to 3 mg./kg. of mixed plastic spheres suspended in a 15 per cent solution of acacia in normal saline were injected under pressure into the supravalvular area of the aorta through a thin-walled Lehman aortographic catheter passed via a femoral or carotid artery. Injection of the spheres was performed during transient cardiac arrest produced by 0.4 mg./kg. of acetylcholine injected intravenously. To make certain of the position of the catheter in the supravalvular area, it was passed while pressure was monitored until a left ventricular pulse appeared on the oscilloscopic screen. The catheter was then withdrawn until an aortic pulse tracing became evident. The usual type of "pull-through" pressure obtained is demonstrated in Figure 1. Figure 2 is an illustration of a peripheral coronary vessel occluded by plastic spheres while Figure 3 demonstrates an area of myocardial infarction produced by this technic.

The method of producing a rise in coronary perfusion pressure consists of obstructing the abdominal aorta with a balloon catheter[11] (Fig. 4). In this manner the circulation was "compartmentalized," leading to a rise in proximal aortic pressure with increased perfusion of the heart and the brain. Blood from the superior vena cava drained by gravity via a Teflon catheter into a Tygon plastic reservoir from where it was pumped by a Sigmamotor pump into the abdominal aorta below the site of obstruction via a femoral artery. As no oxygenator was used, a small priming volume of 150 cc. of blood was adequate.

Obstruction of the abdominal aorta was effected by means of a triple lumen balloon catheter, the center lumen of which opened into a latex balloon, the lumens proximal and distal to the balloon being used for sampling and pressure measurements. This catheter was inserted via a femoral artery to the lowest point of the abdominal aorta at which inflation of the balloon produced a proximal aortic pressure rise. Preliminary experimentation with

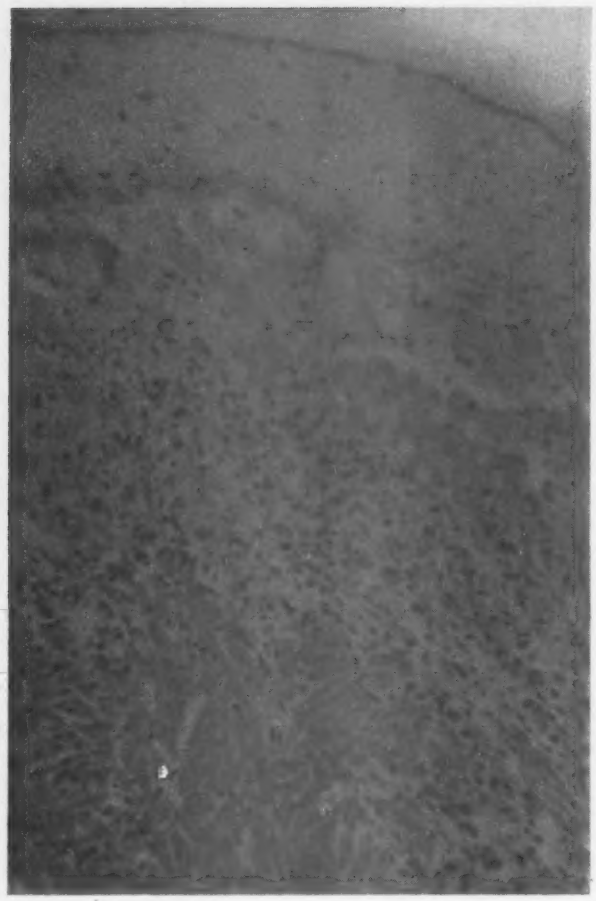

FIG. 3. Photomicrograph of area of myocardial infarction produced by coronary embolization. This section was taken from the apex of the left ventricle in an animal sacrificed ten days after coronary embolization.

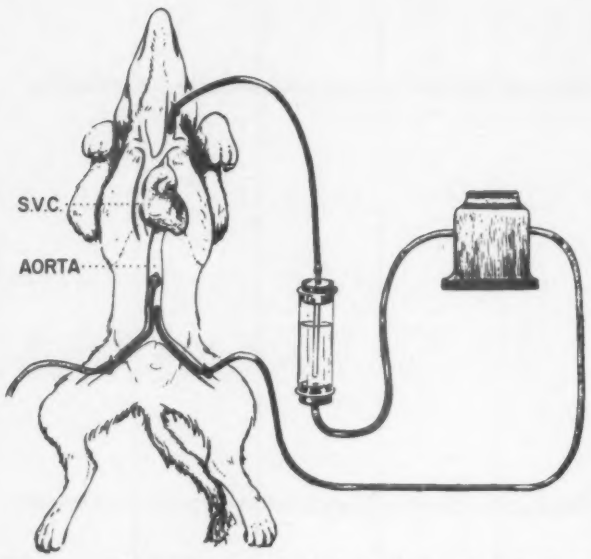

FIG. 4. Schematic representation of the closed chest method in an animal with circulation "compartmentalized" by balloon obstruction of the abdominal aorta. A triple lumen balloon catheter is inserted via a femoral artery to the lowest point of the abdominal aorta at which inflation of the balloon produces a rise in pressure in the proximal aorta. Blood from the superior vena cava drains by gravity into a plastic (Tygon) reservoir from where it is pumped via a femoral artery into the distal aorta below the site of obstruction. (From KUHN et al.[11] *Circulation Res.*, 8: 199, 1960. Reprinted by permission of American Heart Association, Inc.)

the abdomen open demonstrated that it was always possible to achieve this by obstructing the aorta just above the renal arteries, between the renal and superior mesenteric arteries; and occasionally it was possible to obtain a rise in proximal aortic pressure by obstruction below the renal arteries, between the renal and inferior mesenteric arteries.

Determination of aortic pressure (proximal and distal to the balloon), cardiac output, systemic vascular resistance, left ventricular work, left anterior descending coronary inflow, right atrial and left ventricular pressures were performed in the control state (after anesthesia), following coronary embolization before and during extracorporeal circulatory support. Extracorporeal circulatory support was begun approximately thirty minutes after coronary embolization and the procedure was continued until the animal regained control arterial pressures without the aid of extracorporeal circulatory support, as determined by intermittent aortic pressure measurements with the balloon deflated, or until four hours had elapsed from the initiation of the extracorporeal circulatory support. The duration of the experiments ranged from two to four hours.

RESULTS

The results are shown in Table 1 and Figure 5. The data indicate that following coronary embolization there is a profound fall in aortic pressure, averaging 41 per cent, as well as in cardiac output, averaging 50 per cent. Left ventricular diastolic and right atrial mean pressures remain normal, suggesting that there is no significant element of congestive heart failure. As might be expected, coronary inflow falls precipitously, coincident with the decline in coronary perfusion pressure. Of interest is the response of the systemic vascular resistance which shows relatively little change (average–6 per cent fall) despite an appreciable fall in cardiac output, a stimulus which is normally associated with considerable "compensatory" rise in peripheral resistance.

During aortic obstruction and superior vena caval-distal aortic shunting, there is a sharp rise in coronary perfusion pressure (as illustrated in Fig. 6) and the expected accompanying

TABLE 1

Hemodynamic Changes Produced by Coronary Embolization and the Effects of Abdominal Aortic Obstruction and Superior Vena Caval-Distal Aortic Shunting

No. of Dogs		Control before Embolization	Following Coronary Embolization	
			No Circulatory Support	During Aortic Obstruction and SVC-Distal Aortic Shunting
		(Average Values)		
12	Weight (kg.)	23.3		
12	Proximal aortic mean pressure (mm. Hg)	123 (S. D. 21)	73 (S. D. 20)	139 (S. D. 27)
12	Distal aortic mean mean pressure (mm. Hg)	123	73	52
12	Right atrial mean pressure (mm. Hg)	0–5	0–5	0–5
5	Left ventricular end diastolic pressure (mm. Hg)	0–2	0–2	0–2
5	Cardiac output L./min. (cc./min./kg.)	3.33 (126)	1.65 (59)	1.18 (46)
5	Distal aortic shunt flow cc./min. (cc./min./kg.)			572 (30)

rise in coronary inflow, the pressor effect lasting throughout the two to four hour duration of the experiments. There is diminution of the distal aortic pressure. Right atrial mean and left ventricular diastolic pressures remain within normal limits and there is practically no change in left ventricular work (average–8 per cent rise) despite the increase in proximal aortic pressure. This is due to shunting of a portion of the venous return into the distal aorta, thus partially by-passing the heart. The fact that left ventricular work is relatively unchanged despite the rise in coronary perfusion pressure may therefore be attributed to a reduction in "flow" work rather than "pressure" work.

It is of interest that the total body blood flow during extracorporeal circulatory support, as measured by the sum of the shunt flow into the distal aorta plus the cardiac output supplying the proximal aorta, is slightly higher than the postembolic cardiac output before the extracorporeal circulation was started (76 cc./kg./minute as compared to 59 cc./kg./minute).

There is a considerable increase in systemic vascular resistance in the proximal aortic segment, averaging 60 per cent. Since the cardiac output diminishes following coronary embolization, the rise in coronary perfusion pressure during aortic obstruction and superior vena caval-distal aortic shunting is attributable to the mechanically produced rise in vascular resistance in the proximal aortic segment.

COMMENTS

Genesis of Shock Following Myocardial Infarction: Although the precise mechanism for the production of a shocklike state following myocardial infarction is not clear, the data obtained in these experiments are in accord with the view of Agress[13,14] that factors preventing a rise in peripheral vascular resistance in the presence of a considerable reduction of cardiac output are of importance, at least in experimental shock in dogs. Agress has shown that equal reductions of cardiac output may occur in dogs in which shock does or does not develop following experimental myocardial infarction; but in the animals with shock, there

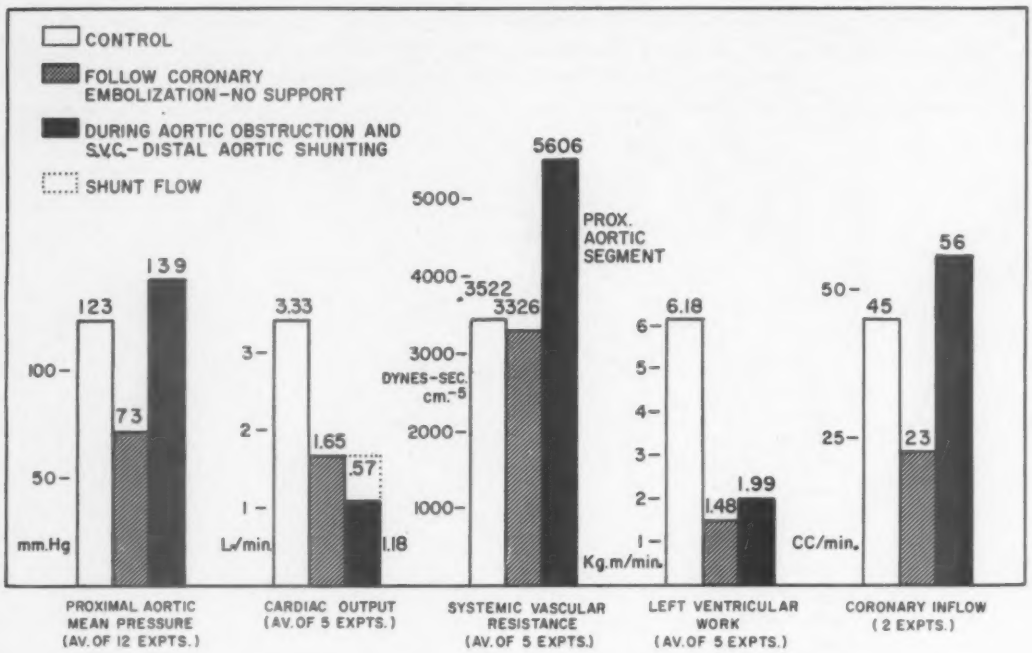

FIG. 5. Hemodynamic changes produced by coronary embolization and the effects of abdominal aortic obstruction and superior vena caval-distal aortic shunting. The white areas indicate control values (after anesthesia); the gray, those following coronary embolization before extracorporeal circulatory support; and the black, those following coronary embolization during aortic obstruction and superior vena caval-distal aortic shunting. Although average figures are presented for graphic purposes, similar changes were noted in each animal. Following coronary embolization, there is an appreciable fall in aortic pressure, cardiac output and left anterior descending coronary inflow, while systemic vascular resistance remains unchanged. During abdominal aortic obstruction and superior vena caval-distal aortic shunting, there is considerable rise in coronary perfusion (central aortic) pressure and coronary inflow, attributable to the mechanical increase in vascular resistance in the proximal aortic segment. Despite this rise in central aortic pressure calculated left ventricular work rises very slightly.

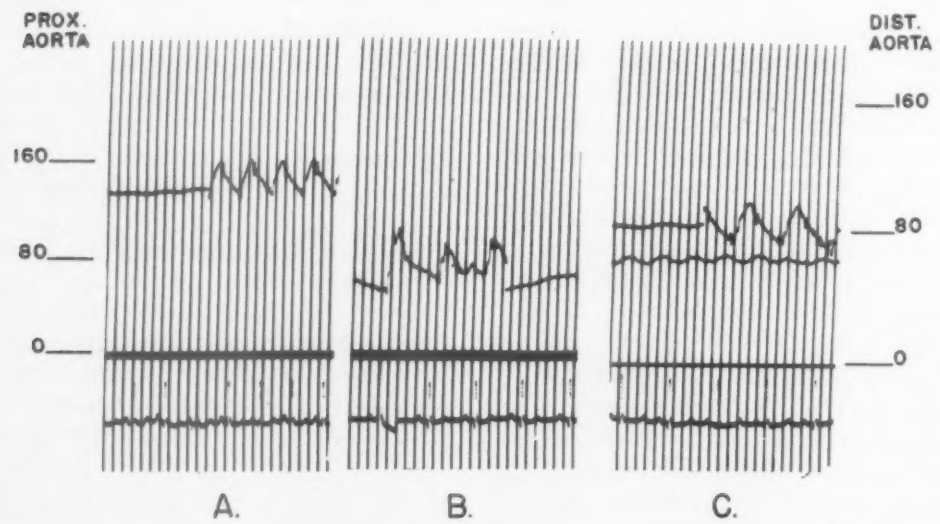

FIG. 6. Aortic pressure recordings. A, control (after anesthesia) mean thoracic aortic pressure is 145 mm. Hg. B, following coronary embolization, mean aortic pressure is 65 mm. Hg. C, abdominal aortic obstruction and superior vena caval-distal aortic shunting causes a rise in thoracic aortic (coronary filling) mean pressure to 115 mm. Hg (upper tracing). Mean distal abdominal aortic pressure, below the site of obstruction (lower tracing), is 55 mm. Hg. (Note different calibration scale for distal aorta.)

is failure of peripheral resistance to rise. In our experiments this observation was confirmed as the peripheral vascular resistance showed no appreciable change (average–6 per cent decrease) following coronary embolization.

The initial physiologic disturbance following myocardial infarction is, as has been shown by several investigators in both human[15–17] and experimental[13,18] myocardial infarction with shock and by the data in these experiments, reduction in cardiac output of considerable degree. The relative importance of the fall in cardiac output and failure of peripheral vascular resistance to rise sufficiently in influencing the development of persistent hypotension following myocardial infarction has not been definitely determined. However, the observations that in experimental myocardial infarction with shock central aortic pressor effects cannot be produced by increasing flow into the aorta by pumping large volumes of blood from the veins to the abdominal aorta,[11] and that considerable increases in proximal aortic and coronary perfusion pressure can be obtained by mechanically increasing vascular resistance in the proximal aortic segment further emphasize the importance of a peripheral resistance factor in the genesis of shock following myocardial infarction.

While it is true that simple venoarterial shunting unaccompanied by a rise in systemic vascular resistance may effectively increase aortic pressure when there is severe congestive heart failure with very little cardiac output, produced by ventricular fibrillation[11] or by pulmonary arterial constriction,[19] this hemodynamic situation is not necessarily present in acute myocardial infarction with shock. In fact, the maintenance of normal right atrial and left ventricular diastolic pressures following coronary embolization suggests that congestive heart failure is not the dominant element, at least in the initial phases, although observations over a more prolonged period might show an eventual rise of left ventricular diastolic pressure.

The conclusions concerning the importance of the systemic vascular resistance in the development of shock following myocardial infarction are in accord with clinical observations demonstrating the efficacy in the treatment of myocardial shock of vasopressor agents which, although possessing some inotropic effect, act primarily to increase systemic vascular resistance. This suggests that maximal vasoconstriction has not occurred despite the considerable fall in cardiac output, normally a stimulus to marked vasoconstriction. Whether the compensatory rise in systemic vascular resistance fails to occur because of a neurogenic mechanism related to diminished cerebral or spinal cord perfusion incident to the lowered cardiac output following myocardial infarction cannot be determined from the available data.

Hemodynamic Effects of Raising Central Aortic Pressure: Of interest is the demonstration that during aortic obstruction and superior vena caval-distal aortic shunting total body blood flow [the sum of the superior vena cava (shunt line) flow and the cardiac output] is greater than the postembolic cardiac output before the start of extracorporeal circulation. This is indicative of an increase in total venous return available for the cardiac output. This may be due to an improvement in cardiac function related to an increase in coronary perfusion pressure or to a change of state of the animals independent of this. In support of the former hypothesis are the experiments of Case and his associates[10] and of Salisbury[9] which demonstrated improvement in the function of both the left[10] and right[9] ventricles when coronary perfusion pressure is increased. Also, in this regard, Herron and his associates[20] have shown an increase in venous return following elevation of arterial pressure with arterenol during extracorporeal circulation for open heart surgery.

The desirability of applying this method of extracorporeal circulatory support to human subjects with myocardial infarction with shock cannot be definitely decided on the basis of the present experiments. In animals with myocardial infarction accompanied by shock it does produce theoretically beneficial hemodynamic alterations. For reasons previously stated, the considerable increase in coronary perfusion pressure attained may be of crucial importance in aiding recovery from the shock-like state as might the increase in cerebral perfusion. In addition, because of shunting of a portion of the venous return from the superior vena cava into the lower aorta, this increase in central aortic pressure is unaccompanied by a significant, concomitant increase in left ventricular work or by alterations in right atrial or left ventricular diastolic pressure to indicate the presence of congestive heart failure. It should be realized, however, that the parameter that is reduced is "flow" work rather than "pressure" work and, therefore, the oxygen needs of the myocardium may be considerably increased by this method of increasing coronary

perfusion. Despite this consideration, clinical experience indicates that survival is increased when the aortic pressure is raised.[12] The net effect of raising central aortic pressure must be assumed to be beneficial regardless of its influence on the oxygen requirements of the myocardium.

Clinical Application: Although no definite statement can be made, the available data suggest that this should be a feasible method to apply to the human subject. The peripheral routes used, a femoral artery and an external jugular vein, are easily accessible and may be rapidly cannulated after relatively simple surgery under local anesthesia. The system can be rapidly assembled as it requires a small priming volume and therefore there is no need for large volumes of fresh blood. The disadvantages of oxygenation, with its attendant trauma to the blood elements, associated larger priming volumes and, in some systems, microbubbles, are eliminated; although for prolonged perfusions the blood could be oxygenated before it is returned to the distal aorta. Our previously reported data concerning arteriovenous oxygen differences in the upper and lower portions of the body of normal dogs in which this method was utilized[11] did demonstrate some widening of the distal aortic-inferior vena caval oxygen difference at the end of four hours of circulation although the data were not conclusive. Prolonged perfusions therefore will probably require oxygenation.

Possible Dangers of Method: The oxygen needs of the distal portion of the body, below the site of the aortic obstruction, are probably relatively small, although it is not known at this time whether they would be met by this method of extracorporeal circulatory support applied for a prolonged period even if an oxygenator were added to the circuit. There are, however, some observations to indicate that these flow requirements may not present an insoluble problem apart from that offered by the requirements of the kidneys. That the oxygen needs of the posterior or distal portion of the body of the unanesthetized dog are relatively small has been demonstrated by Levy and Blalock[21] who determined that the oxygen consumption of the kidneys and the areas distal to them was 17 per cent of the total oxygen consumption whereas these areas received about 32 per cent of the total blood flow. The area distal to the kidneys accounts for about 12 per cent of the total oxygen consumption. Paneth and associates[22] have shown that the oxygen needs of all of the tissues of the inferior vena caval system can be met by a total flow of about one-half the basal cardiac output. The bulk of these needs, according to Levy and Blalock,[21] is accounted for by the liver and portal system, arterial supply to which is above the aortic obstruction in our preparation. Hamer and his associates[23] have successfully shunted unoxygenated blood from the superior vena cava into the unobstructed abdominal aorta for fifty-two hours in a dog and for twenty-six hours in a human.

Of concern in the application of this method is the diminution in renal function in those animals with suprarenal aortic obstruction. Although our previous studies in normal dogs demonstrated that some degree of glomerular filtration was maintained with the distal aortic flows obtained, that glomerular filtration rapidly returned toward normal in the postperfusion period and that there was no azotemia for periods up to twenty-four hours following the procedure,[11] renal function was consistently reduced. One would expect an even further reduction in myocardial infarction with shock. Adjustment of the height of the reservoir draining the superior vena cava may, to some extent, increase or diminish the flow into the distal aorta. Current investigation is being conducted into the effects of blood stream cooling used concomitantly with aortic obstruction in an effort to "protect" the relatively ischemic area below the site of obstruction by diminishing its oxygen requirements.

Blood cell destruction with prolonged pumping is also a factor of potential concern. While it is difficult to translate the effects on dog blood to a clinical situation in humans, our previous experiments in dogs during six hours of veno-arterial pumping[11] showed a tolerable degree of hemolysis, and others, utilizing a different type of pump,[23] have shown negligible hemolysis after sixteen hours of pumping in a human subject.

The crucial question, which at this stage is unanswered, is the duration of circulatory support which would be needed in an individual with myocardial infarction with shock. This can be expected to be somewhat variable. Although it would seem that considerably prolonged support would be necessary, sufficient improvement in myocardial function and cerebral perfusion may occur when coronary perfusion is significantly increased so that relatively

short perfusions, for a feasible period of time, would be required before responsiveness to drugs or natural homeostatic mechanisms are restored.

Summary

The hemodynamic effects of extracorporeal circulatory support were investigated in closed chest dogs with myocardial infarction with shock produced by coronary embolization. Determinations of cardiac output, coronary perfusion (central aortic) pressure, systemic vascular resistance, left ventricular work, right atrial and left ventricular pressures were performed in the control state, following coronary embolization prior to extracorporeal circulatory support and following coronary embolization during two to four hours of extracorporeal circulatory support.

Although there was diminution in cardiac output following coronary embolization, systemic vascular resistance did not rise appreciably and hence there was considerable arterial hypotension. Pumping of large volumes of blood from the venae cavae into the abdominal aorta did not produce a rise in central aortic pressure and increase of coronary perfusion. To increase coronary perfusion pressure with the aid of extracorporeal circulation it was necessary to increase systemic vascular resistance. This was achieved by obstruction of the abdominal aorta with a balloon catheter introduced via a femoral artery, the distal aorta below the site of obstruction being supplied with blood pumped from the superior vena cava.

This method of mechanically increasing systemic vascular resistance required a small priming volume and relatively simple peripheral cannulations. A sustained rise in coronary perfusion (central aortic) pressure was produced which was unassociated with significant increases in right atrial or left ventricular diastolic pressures or in calculated left ventricular work.

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Physiologic Principles of Partial Extracorporeal Circulation for Mechanical Assistance to the Failing Heart*

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MECHANICAL METHODS of assistance to the failing heart are much discussed in clinical circles and there is little doubt that some forms of "assisted circulation" will soon be utilized. One of the more promising methods is partial heart-lung bypass. As physiologists, our work in the laboratory has revealed the following: (1) Extracorporeal circulation, in the form of partial heart-lung bypass, is presently feasible and well tolerated in dogs for periods up to ten hours.[1] (2) Much more fundamental knowledge still needs to be acquired before a safe clinical application is possible.

METHOD

The circulatory situation prevailing during partial heart-lung bypass, or "parallel blood circulation" as it was originally called in 1929 by Brukhonenko,[2] is depicted in Figure 1. One portion of the blood flows through the heart and lungs; the other portion is drained into the extracorporeal circuit, oxygenated in the artificial gas exchange device and then pumped back into the arterial tree. Before partial heart-lung bypass is instituted the entire perfusion of the body tissues is supplied by the cardiac output. During partial heart-lung bypass, the total tissue perfusion is provided by two sources of arterialized blood: the left ventricular output derived from the reduced pulmonary flow plus the extracorporeal flow.

It has been demonstrated empirically that under conditions of heart-lung bypass of short duration, perfusion flows below the normal cardiac output can be tolerated by the organism without permanent damage. A reduction in distribution of oxygen to the tissues because of diminished perfusion flow results in a metabolic acidosis. However, from the practical point of view a thirty to sixty minute period of relative hypoxia does not seem to jeopardize the cellular metabolism irreversibly. After bypass the organism is able to compensate for the accumulation of acid products by a higher consumption of oxygen. This extra oxygen uptake represents the payment of an oxygen debt incurred during the period of inadequate perfusion of the tissues. The metabolic state is somewhat similar to that encountered after muscular exercise. Unfortunately, measurements of oxygen debt under conditions of cardiopulmonary bypass, such as Hill's classic measurements of oxygen debt after exercise, have not been reported.

Obviously, there is a limit to the oxygen debt which an organism can tolerate and, therefore, to the duration of heavy exercise. Similarly, there is a limit to the amount of acid metabolites which an organism can eliminate successfully after inadequate perfusion. Therefore, consideration for the oxygen distribution to the tissues becomes the primary concern in perfusions exceeding one or two hours. It is classically admitted that at a constant temperature the basal oxygen requirement of the tissues is independent of the amount of oxygen actually distributed by the blood. Thus, the main physiologic problem of a steady and smooth partial heart-lung bypass is to arrange the blood flow to the natural and to the artificial lung in such a way that enough oxygen is picked up to meet the requirements of the tissues. One aspect of this problem is the volume of blood

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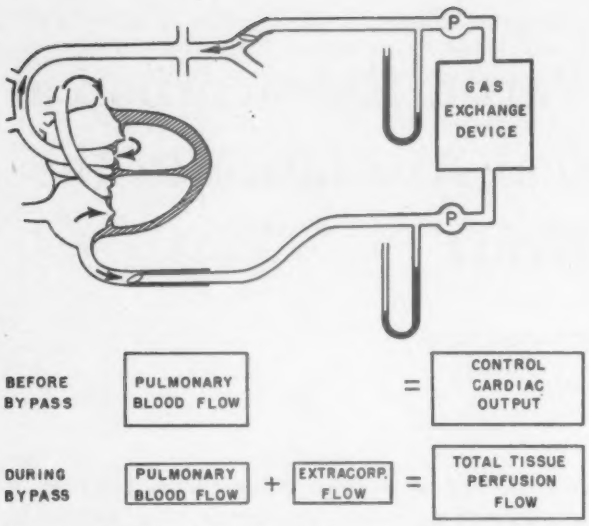

FIG. 1. Schematic representation of partial heart-lung bypass. The heart is on the left side of the figure, the extracorporeal circulation on the right. One part of the venous blood returns to the right side of the heart, the other part is drained by a pump (P) into the extracorporeal circuit. The arterial tree is filled simultaneously by the left ventricle and by a pump (P) from the gas exchange device.

available for gas exchanges in the pulmonary vascular bed and in the artificial oxygenator; another is the reaction of the lungs to the condition of permanently decreased pulmonary blood flow, when part of the venous return is diverted into the extracorporeal circuit.

This study is restricted to the clarification of two problems important for future clinical application, the regulation of cardiac output and the regulation of pulmonary ventilation.

EXPERIMENTAL OBSERVATIONS

REGULATION OF CARDIAC OUTPUT

The aim of partial heart-lung bypass is to reduce the work load of the heart. This may be done by reducing the heart rate, the stroke volume and the mean arterial pressure while the artificial circuit secures the distribution of blood to the body tissues.

The adjustment of cardiac output to the conditions of decreased venous return results from a complex interrelationship of extra-

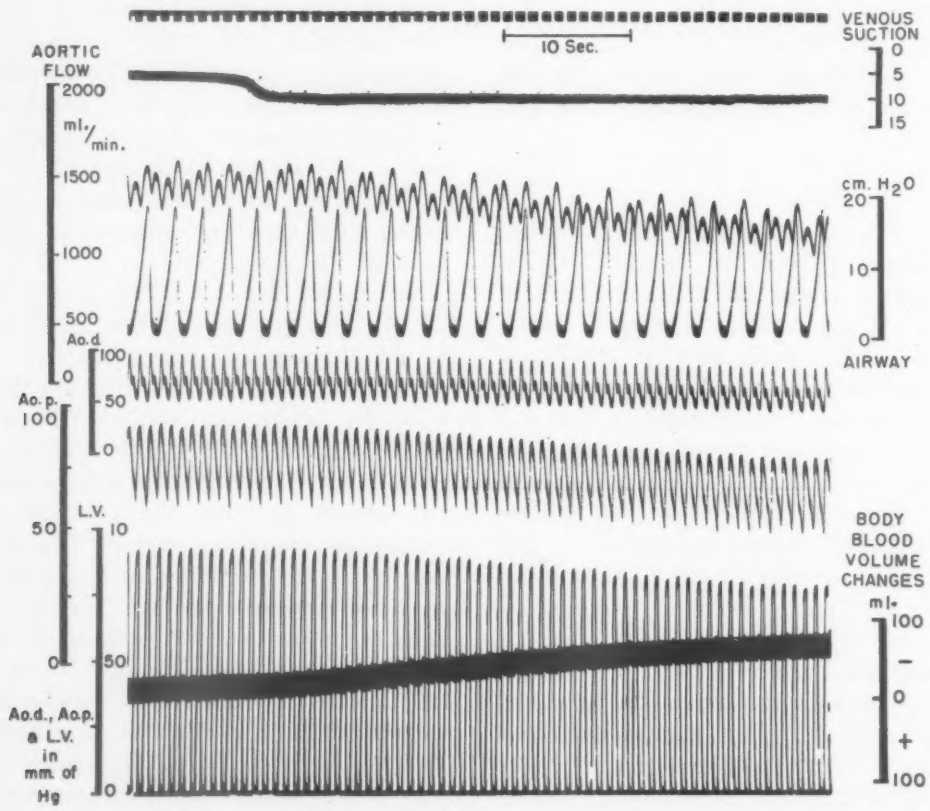

FIG. 2. Cardiac output and systemic blood volume as affected by an increase of the rate of extracorporeal flow from 300 to 400 ml./minute. *Tracings from top to bottom:* Time is expressed in seconds; venous suction in cm. H_2O; aortic flow (left ventricular output minus coronary flow) in ml./minute; airway pressure in cm. H_2O; distal aortic pressure in mm. Hg; proximal aortic pressure in mm. Hg; left ventricular pressure in mm. Hg; changes in body blood volume from control value (0) in ml.

corporeal blood flow, systemic blood volume and pulmonary blood flow. The following series of three experiments demonstrates this interdependence.

1. *At a given extracorporeal blood flow*, it is primarily the volume of the systemic blood which determines the magnitude of the cardiac output. This feature is illustrated in experiments in which changes in rate of extracorporeal flow, cardiac output and systemic blood content are simultaneously recorded (Fig. 2). When the rate of extracorporeal flow is suddenly increased from 300 to 400 ml./minute, the aortic flow decreases from 1,480 to 1,060 ml./minute. The reduction in cardiac output exceeds the augmentation of extracorporeal flow because the systemic blood volume diminishes; the increase in "venous suction," while the arterial infusion pressure remains constant, causes a shift of blood from the organism into the extracorporeal circuit. The volume of blood displaced during the period of recording depicted in Figure 2 is 70 ml. The same dependency of cardiac output upon systemic blood content is maintained after a steady state of flow has been reached in both the external and body circuits. The total systemic perfusion (cardiac output plus extracorporeal flow) is increased above control level when blood is administered to the animal. It remains below the control level when blood is shifted from the organism into the external gas exchange device.[3]

2. *At constant volume of systemic blood*, stepwise increments in extracorporeal blood flow induce proportional decrements in pulmonary blood flow (Fig. 3). The total tissue perfusion remains unchanged if care is devoted to maintain the systemic blood volume constant during the entire period of perfusion. The metabolic requirements of the tissues are fulfilled; consequently, acidosis does not develop within a period of two to three hours. Increasing the extracorporeal flow under such conditions simply shifts the functional load of gas exchanges from the natural lung to the artificial lung. At both sites the exchanges remain fully efficient. The total oxygen uptake (lung and heart-lung machine) is equal to the control values.[4]

3. *When the volume of systemic blood and the extracorporeal flow are modified simultaneously* the changes in cardiac output are necessarily more complex. Such a situation prevails when no exact control of the content of systemic blood can be exercised because the variations of blood content in the heart-lung machine do not truly reflect variations of the systemic blood volume. The changes in cardiac output then depend upon how much blood is shifted from the body

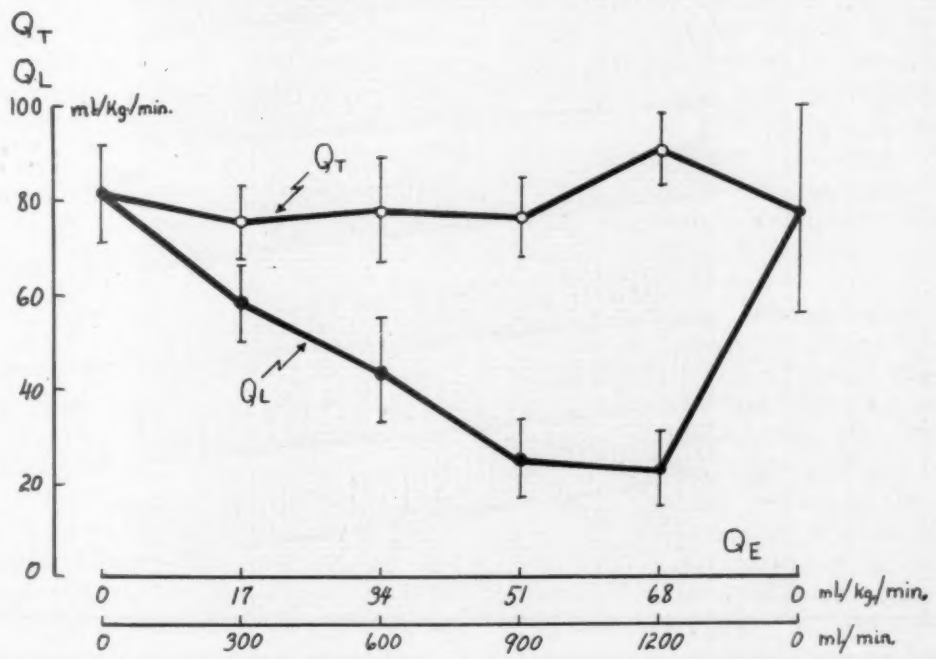

FIG. 3. The effect of increasing extracorporeal flow rates (Q_E) on the pulmonary blood flow (Q_L) and the total tissue perfusion flow (Q_T). In these experiments the systemic blood volume is kept constant.

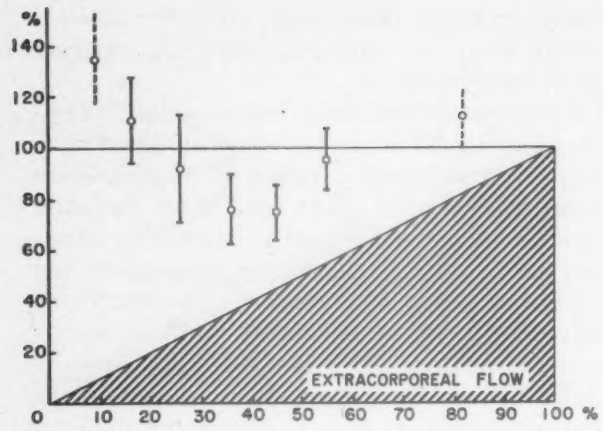

FIG. 4. The effect of increasing the rate of extracorporeal flow on total tissue perfusion flow. The systemic blood volume is not kept constant but permitted to vary to maintain the mean aortic blood pressure close to the control value. The flow values are expressed in per cent of the control cardiac output. The hatched triangle represents the increasing contribution of extracorporeal flow to the total tissue perfusion.

into the extracorporeal circuit (or vice versa) as the extracorporeal flow is increased. The cardiac output is almost unaffected when less than 15 per cent of the control venous return is deviated into the extracorporeal circuit. On the other hand, extracorporeal flow in the range of 40 to 50 per cent of the control cardiac output may be associated with marked reductions in pulmonary blood flow. This probably occurs because of partial exsanguination of the animal into the heart-lung machine. However, there is no further decrease in pulmonary blood flow when the extracorporeal flow reaches 70 per cent or more of the control cardiac output. The persistance of a sizable ventricular output despite a high rate of extracorporeal flow is characteristic of animals during closed-chest surgery. It is practically impossible to drain all the venous blood into the heart-lung machine by the usual peripheral cannulation. In contrast, the cardiac output of animals undergoing open-chest surgery can be

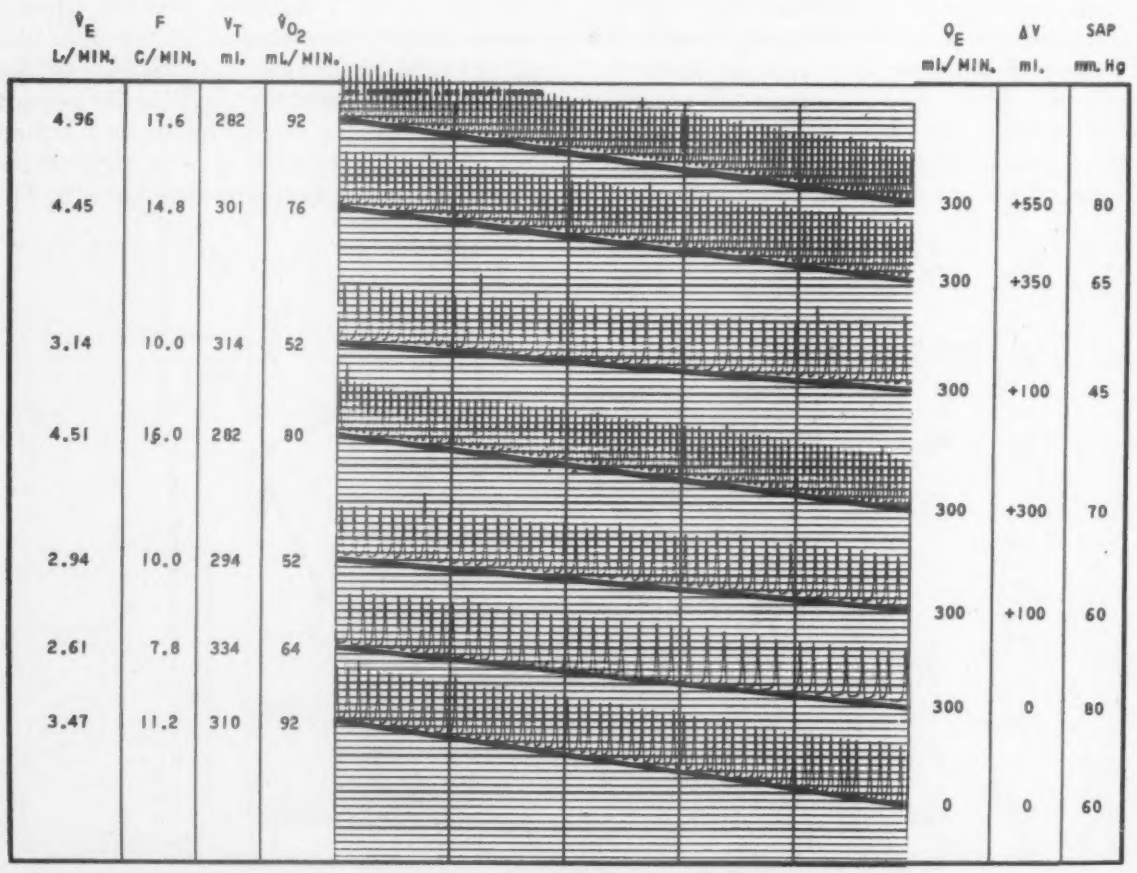

FIG. 5. Spirometer record of pulmonary ventilation (V_E) and oxygen uptake (V_{O_2}) in the lungs as affected by changes in body blood volume (ΔV) during partial heart-lung bypass. After the control recording (bottom tracing) the extracorporeal flow rate (Q_E) was maintained constant at 300 ml./minute. F = respiratory rate; V_T = tidal volume; SAP = systemic arterial pressure (mean).

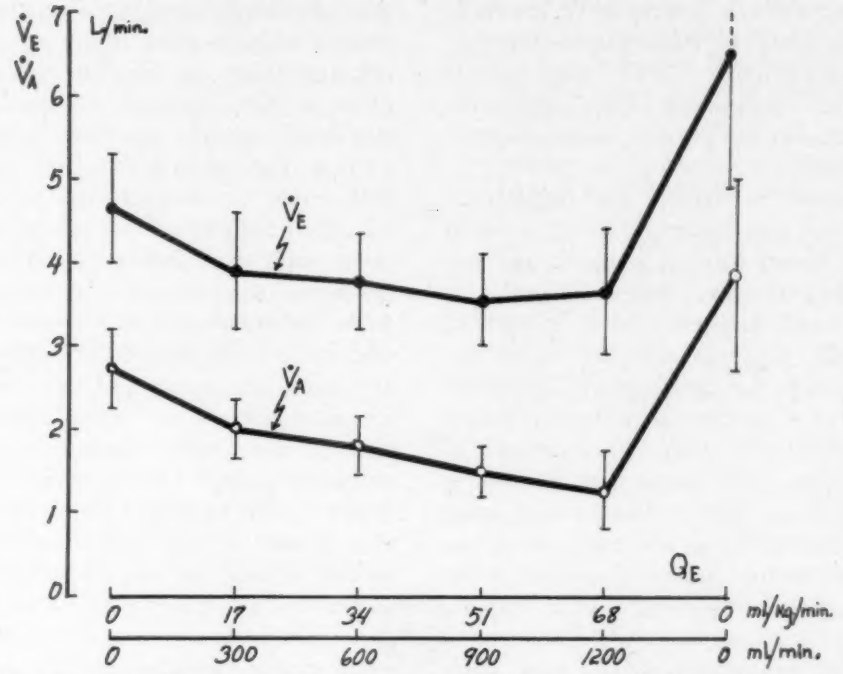

FIG. 6. The effect of increasing extracorporeal flow rates (Q_E) on pulmonary ventilation (V_E) and alveolar ventilation (V_A). In these experiments the systemic blood volume is maintained constant.

reduced to zero with central cannulation. It has been our experience with dogs during closed-chest surgery that only those animals which have a large blood volume or have received a transfusion have enough venous blood available for drainage to permit extracorporeal flow rates above 65 ml./kg./minute. The relationship of total tissue perfusion to extracorporeal rate of flow under these conditions[5] is illustrated in Figure 4.

REGULATION OF PULMONARY VENTILATION

When the pulmonary blood flow is reduced during partial heart-lung bypass, dogs breathing spontaneously tend to ventilate less. Whereas one can modify the amount of pulmonary blood flow by changing the extracorporeal flow, the systemic blood content, or both, the pulmonary ventilation remains under the control of the supposedly intact respiratory centers.[6] Our observations reveal that the depression of the pulmonary ventilation is also related to the systemic blood volume and to the rate of extracorporeal flow. These relationships are demonstrated in two series of experiments with spontaneously breathing dogs as follows:

1. *At constant extracorporeal flow* the pulmonary ventilation increases when the systemic blood volume (and consequently the pulmonary blood flow and the pulmonary blood volume) is increased. The variations of the pulmonary ventilation are mainly due to changes in respiratory frequency. The tidal volume remains practically unchanged. The ventilatory adaptation to transfusion and bleeding during partial heart-lung bypass is illustrated in Figure 5. Increases in blood volume (ΔV) are consistently associated with increases in ventilation (V_E). Withdrawal of the transfused blood depresses the ventilation. Parallel variations of pulmonary oxygen uptake and pulmonary ventilation indicate that the spontaneous ventilation follows the changes in pulmonary blood flow.

2. *At a constant blood volume*, the correlation between pulmonary ventilation and pulmonary blood flow becomes apparent when the extracorporeal flow rate is increased stepwise. Under these conditions the ventilation decreases as the extracorporeal flow increases and, consequently, the pulmonary blood flow decreases. The relative decline of ventilation (Fig. 6) is more marked if the alveolar ventilation (V_A) is considered rather than the total ventilation (V_E). When the extracorporeal flow is enhanced more than 70 per cent of the control cardiac output there is no further reduction in ventilation. In fact, a few dogs exhibit a marked hyperventilation when the

pulmonary blood flow is appreciably lowered. We have no satisfactory explanation for this particular phenomenon. After the partial heart-lung bypass procedure, the pulmonary ventilation returns to the control values or may even exceed them.[4]

The mechanisms by which the respiratory centers depress the pulmonary ventilation when the pulmonary blood flow is reduced are not known at the present time. Arterial blood pH, carbon dioxide and oxygen partial pressures, blood and body temperatures are essentially unchanged during the perfusion procedure. Therefore, they offer no clues as to the regulatory mechanisms involved. The association of ventilatory changes with maneuvers modifying the pulmonary blood flow indicates that some kind of stretch receptors in the atria or in the pulmonary vascular bed may be involved in the respiratory changes observed. Our experiments do not provide any definite information concerning the respiratory drives and their pathways at present.

Comments

These experiments demonstrate that unless one controls the systemic blood volume one cannot distribute the blood flow between extracorporeal and intracorporeal circuits to maintain an adequate perfusion of all body tissues. Under these conditions of partial heart-lung bypass the volemia regulates the pulmonary blood flow as well as influencing the pulmonary ventilation. Thus, to be adequate from both hemodynamic and metabolic viewpoints a procedure of mechanical assistance to the failing heart must involve the circulatory and respiratory functions. One cannot deal exclusively with the one organ whose work load one wants to reduce. The effect of the intended therapeutic maneuvers upon the organism as a whole must be considered.

It should be borne in mind that extracorporeal circulation procedures create highly artificial conditions in the body. By an appropriate design of the circuits it is possible to produce almost any potentially beneficial or detrimental hemodynamic situation to the heart. The experimenter is, therefore, tempted to use some form of extracorporeal circulation to correct the signs of artificially induced cardiac failure. Lately, many experiments have been reported using this approach to evaluate the benefits of assisted circulation. It has been demonstrated that most of the abnormal conditions of pressures and flow induced by mechanical means such as obstruction of vessels, valvular regurgitation or creation of shunts can be relieved by artificial circulation procedures. All that is needed is a circuit which will either bypass the obstruction or the valvular insufficiency, or abrogate the burden of a shunt by another shunt in reverse direction.

In such experimental studies measurements restricted to pressures and flow usually furnish little information which could not have been obtained from hydraulic models. Therefore, the creation and relief of artificial forms of cardiac failures by extracorporeal circulation technic may easily become a pointless "hemodynamic game." For instance, right ventricular failure could be produced by an acute stenosis of the trunk of the pulmonary artery and the overdistension of the chambers of the right side of the heart then relieved by a right heart bypass. It is doubtful whether the organism will ever derive greater benefit from the extracorporeal circulation procedure than from simply removing the stenosis.

In fact, methods of circulatory assistance may be so effective in correcting abnormal values of pressures in artificially induced cardiac failure that measurements of pressures alone offer no valid criterion for evaluating the benefits of the assistance. Much more meaningful is information relative to flow, contractile force of the myocardium, state of vasomotor tone and metabolic adequacy of the circulatory conditions. Such data are surprisingly scarce in the few reports of experimental or clinical use of circulatory assistance in cardiac failure. This lack of physiologic knowledge may explain the still unpredictable outcome of the extracorporeal circulation procedures when used for many hours in complex pathologic cardiocirculatory conditions.

Summary

Partial heart-lung bypass is one form of artificial circulation proposed for assisting the failing heart. Since it involves extracorporeal gas exchanges, respiratory as well as circulatory functions must be considered during the procedure. Our studies reveal that an accurate knowledge of the systemic blood volume is necessary to control the distribution of blood flow between the intracorporeal and extracorporeal circuits. The systemic blood content also influences the pulmonary ventilation. Partial heart-lung bypass can be performed in

such a manner that it completely fulfills the metabolic requirements of the body tissues. Whether abnormal hemodynamic conditions in heart failure can be relieved by partial heart-lung bypass after the period of active circulatory assistance is still to be evaluated.

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Review

Two Step Exercise Test as a Test of Cardiac Function in Chronic Rheumatic Heart Disease and in Arteriosclerotic Heart Disease with Old Myocardial Infarction*

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In the original description of a standard two step functional test of the heart by Master and Oppenheimer,[1] the functional status of the circulatory system was considered adequate if the blood pressure and pulse rate returned to control values within two minutes. Subsequently the electrocardiogram was added to the test,[2] and attention was focused upon changes in this parameter. Since then the electrocardiographic response to the test has been used primarily in the differential diagnosis and early detection of coronary artery disease rather than as a nonspecific functional test of the heart.

Considerable disagreement has arisen regarding the indications for the performance of this test and the criteria for an abnormal response. Many authorities have stated that the presence of an abnormal electrocardiogram at rest contraindicated the performance of this exercise.[3–5] However, the two step test has been used at the Cleveland Work Classification Clinic for the past nine years as a measure of circulatory function in patients with all types of heart disease.[6] The results of the two step test were found to be valuable in the counseling of subjects with heart disease in regard to work and ordinary daily activities, since it provided useful information about the circulatory response to a peak effort. The sound physiologic basis of this test was later demonstrated by Ford and Hellerstein[7] when the energy cost was measured and found to be the same (8.5 calories per minute) for all persons regardless of age, height or weight.

The current controversy over the electrocardiographic criteria of an abnormal response to the exercise test stems from the attempt to distinguish those electrocardiographic changes due to coronary artery disease from "false-positive" changes.[3] Although commonly accepted, this distinction has not yet been firmly established. We have noted similar changes in mechanism, conduction and repolarization after exercise in more than 1,700 patients with all types of heart disease.[8] Similar changes have been described by others in patients with neurocirculatory asthenia,[9] in selected patients with rheumatic heart disease,[10–12] patients with paroxysmal arrhythmias,[13] the physically unfit[14] and "normal" women.[3,15]

The present study was designed to test whether the electrocardiographic response to the two step test is diagnostic or specific for coronary artery disease, or rather, whether it reflects circulatory sufficiency. Since there have

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been no systematic studies on the electrocardiographic response to this exercise test in unselected patients with rheumatic heart disease, we have analyzed and compared the response of patients with chronic valvular rheumatic heart disease without clinical or electrocardiographic evidence of coronary disease with that of patients with known previous myocardial infarcts. The responses were evaluated according to five sets of electrocardiographic criteria.[16–18]

Methods

After preliminary evaluation of the medical history, physical examination, vital capacity, resting electrocardiogram, response to the Valsalva maneuver (Flack test)[19–21] and the longitudinal ballistocardiogram, patients attending the Work Classification Clinic of The Cleveland Area Heart Society routinely perform a standard two step exercise test[2,16] unless contraindicated. Contraindications to the performance of the two step exercise test include: (1) frank congestive heart failure, (2) evidence of impending or recent myocardial infarction (within three months), (3) angina decubitus, (4) uncompensated arrhythmias and (5) general debility. Twelve lead electrocardiograms are taken before, immediately after, two minutes and five minutes after the subject performs a single two step test in the period of a minute and a half as described by Master.[2,16] The double standard test[22] has been proscribed since it is our opinion that maximal or submaximal effort tests are contraindicated for patients with coronary disease except in special circumstances. The test is performed with a physician in attendance and is stopped at the appearance of pain, marked venous distention, premature beats, excessive tachycardia (above 150), bradycardia, A-V block or respiratory distress. With these precautions in force, the test has been performed in the past nine years at the Cleveland Work Classification Clinic by more than 1,700 patient without untoward incident.

The records of 192 patients were selected for analysis: (1) ninety-two consecutive patients with a diagnosis of rheumatic heart disease and (2) 100 consecutive patients with confirmed histories of previous myocardial infarction, but not receiving a digitalis preparation. Because digitalis itself produces changes in the ST-T complex of the electrocardiogram,[23] the patients with rheumatic heart disease were evaluated in two groups: (1) those taking digitalis (forty-two patients) and (2) those not receiving digitalis (fifty patients). In addition, the electrocardiographic and pulse rate response to the Valsalva maneuver (Flack test) was obtained in eighty of the ninety-two patients with rheumatic heart disease. While in the sitting position the patient achieved forced expiration from inspiratory midposition against 40 to 60 mm. Hg pressure (blowing into a mercury manometer)

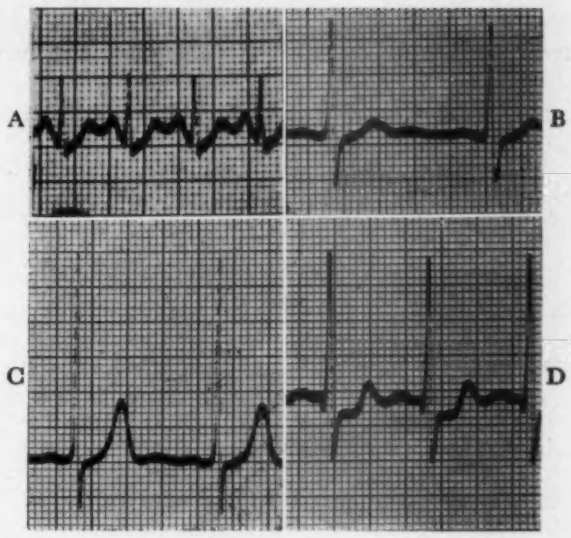


Fig. 1. Types of depression of the S-T segment in electrocardiograms immediately after exercise. A, depression of the S-T (J) junction of 0.5 mm. below the P-R segment in lead II associated with tachycardia, a descending P-R interval and large P waves. This is abnormal according to Master's criteria but is spurious according to other criteria. B, depression of the S-T (J) junction of 0.5 mm. in V_4 without a sloping P-R segment, large P waves or tachycardia. This is abnormal according to Master's and our criteria. C, depression of the S-T (J) junction of 0.5 mm. in V_4 with horizontal depression of the S-T segment before ascending into the T wave. This is abnormal according to Master's, Myers' and Talmers', and our criteria. D, depression of the S-T segment of 2.5 mm. with return to the isoelectric line occurring in the latter half of the Q-T interval. This is abnormal according to all criteria.

for twelve to fifteen seconds. Lead II of the electrocardiogram was taken continuously during the maneuver and for twenty to thirty seconds thereafter. The response was considered abnormal if the pulse ate failed to increase during the period of sustained increase of intrathoracic pressure, if the pulse rate did not slow abruptly within eight beats or six seconds after the maneuver, or if electrocardiographic abnormalities occurred.[19–21,24]

Analysis of Electrocardiographic Changes

A detailed analysis of the twelve lead electrocardiograms taken before and after exercise was made independently by each of us and rechecked independently and subsequently together. Changes in the following features were noted, quantitated when possible and tabulated on code sheets to facilitate statistical analysis: (1) mechanism; (2) intraatrial, atrioventricular and intraventricular conduction; (3) magnitude, direction and sense of the vectors of the QRS complex and the ST-T complex with its component vectors (S-T junction, S-T segment and T wave) of the ventricular gradient;[25–27] (4) angles between QRS and T and between QRS and the ventricular gradient;[28] (5) the effective vector of

TABLE I

Incidence of Abnormal Electrocardiographic Responses to Exercise (According to Various Criteria) in Fifty Subjects with Rheumatic Heart Disease but not Receiving Digitalis

Electrocardiographic Change	No. of Patients	Criteria				
		Master[16,17]		Myers and Talmers[18]	Lepeschkin and Surawicz[3]	Ours
		1950	1957			
1. Change in mechanism	3	3	0	0	0	3
2. Depression of the S-T (J) junction of:						
(a) 0.5 mm. below the horizontal extension of the P-R segment	2	2	2	0	0	0
(b) 0.5 mm. below the extension of the slope of the P-R segment	4	4	4	0	0	4
3. Depression of the S-T segment of:						
(a) 0.5 to 0.74 mm.	1	1	1	1	0	1
(b) 0.75 to 1.0 mm.	2	2	2	2	2	2
(c) greater than 1.0 mm.	4	4	4	4	4	4
4. Change of 25 degrees or more in the QRS-T angle	1	0	0	0	0	1
5. Increase in magnitude of an abnormal T vector	1	0	0	0	0	1
6. 1 and 2	1	1	1	0	0	1
7. 2 and 4	2	2	2	0	0	2
8. 3 and 4	2	2	2	2	2	2
9. 1, 3 and 5	1	1	1	1	1	1
10. 1, 3 and 4	1	1	1	1	0	1
Total no.	25	23	20	11	9	23
Per cent	50	46	40	22	18	46

exercise;[20] and (6) U waves. Distinction was made between primary T wave changes and those secondary to a change in the QRS complex.[25–27] The level of the S-T junction was measured in reference to the end of the Ta (P-R) segment, i.e., before the beginning of the QRS, in two ways: (1) horizontal extension of the end of the Ta segment and (2) extension of the end of the Ta segment according to the method of Lepeschkin and Surawicz[3] to obviate false displacement of the S-T junction or even of the S-T segment by a large wave of atrial repolarization[3] (Fig. 1).

CRITERIA OF ABNORMAL RESPONSE

The responses were classified as normal or abnormal by five sets of criteria: (1) Master's in 1950[16] and (2) in 1957;[17] (3) Myers' and Talmers';[18] (4) Lepeschkin's and Surawicz';[3] and (5) ours.

1. In 1950, Master[16] used leads I, II, III and V_4 and judged a response abnormal on the basis of (1) depression of the RS-T segment of 0.5 mm. below the P-R segment in any lead; (2) a change from an upright to an isoelectric (flat) or inverted T wave and a change in the opposite direction from an inverted to a flat or upright T wave; (3) premature beats or some more significant arrhythmia, widening of the QRS, intraventricular or bundle branch block, large Q waves, prolongation of the P-R interval or heart block.

2. In 1957, Master[17] revised his criteria and his electrocardiographic lead selection, using only one limb lead, lead II, and leads V_4, V_5 and V_6 or leads V_3, V_4 and V_5, instead of V_4 alone. RS-T depression of more than 0.5 mm. below the P-R segment in any of these leads is considered an abnormal response. Minor T wave changes alone are of no or little significance according to Master, although "definite T wave inversion is probably abnormal." Transient arrhythmias or prolonged intraventricular conduction are "also of no or little diagnostic import."

3. Myers and Talmers[18] state that S-T segment abnormality should be based on the S-T segment configuration, i.e., remaining horizontally depressed before ascending into the early limb of the T wave, as well as the degree (0.5 mm.) of depression. Inverted T waves in normal subjects may be distinguished by the associated shortening of the Q-R interval or by the use of ergotamine to prevent the T wave inversion. Ectopic beats or rhythms appearing only after exercise are considered to be suggestive of myocardial ischemia, although this diagnosis is not made by Myers and Talmers in the absence of other abnormalities (i.e., of S-T or QRS).

4. The criteria of Lepeschkin and Surawicz[3] include: (1) inversion of the T wave in lead I or depression of the S-T segment junction beyond the continuation of the P-R interval of 0.75 mm. or more; (2) return of the S-T segment to the baseline

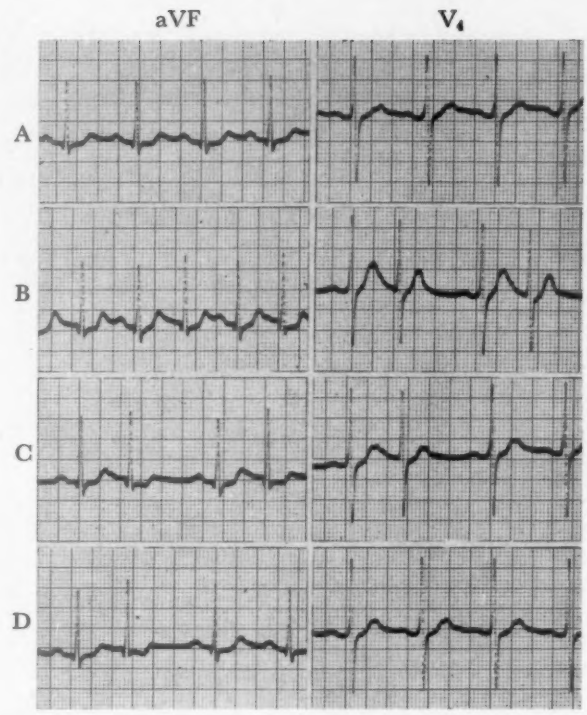


FIG. 2. Atrial premature beats and S-T segment displacement, an abnormal electrocardiographic response to exercise of a patient with rheumatic heart disease, not receiving digitalis. The patient (W. S.) was a thirty-four year old man with left ventricular hypertrophy, predominant aortic insufficiency and slight aortic stenosis and mitral insufficiency; therapeutic and functional classification, IIB. A, control. B, immediately after exercise atrial premature beats appeared, forming a bigeminy and showing 1.5 mm. S-T depression. In the sinus beats the S-T segment is depressed 1.0 mm. C and D, two and five minutes later, respectively, also show greater S-T segment depression in the atrial premature beats.

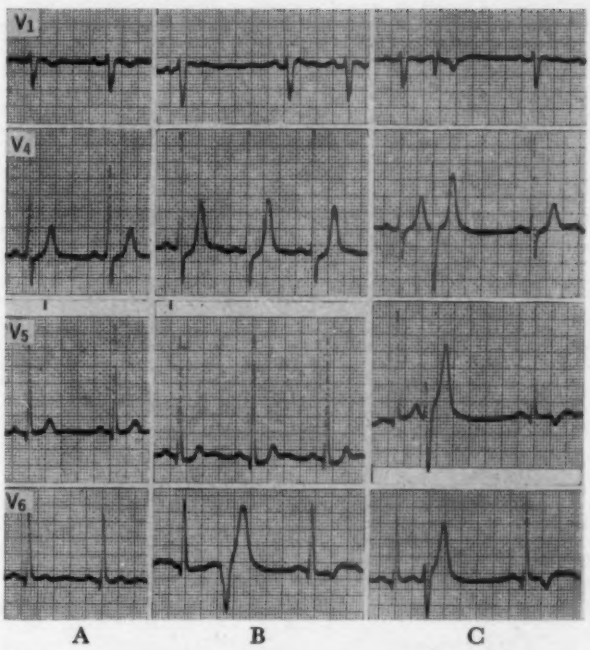


FIG. 3. Abnormal electrocardiographic response to exercise of an asymptomatic patient with rheumatic heart disease resembling that found in a patient with coronary artery disease. The patient (S. D.) was a twenty-two year old stevedore with insufficiency of the mitral and aortic valves and left ventricular hypertrophy; therapeutic and functional classification, IA. He was not receiving digitalis medication. A, control record. B, immediately after exercise. C, five minutes later. After exercise, significant displacement of S-T junction and S-T segment and frequent posterior left ventricular premature beats appeared transiently, forming a bigeminy with postextrasystolic T wave inversion in leads aVF (not shown here), V_5 and V_6. The patient experienced mild shortness of breath.

taking place in the second half of the Q-T interval; and (3) S-T segment depression of 0.5 mm. or more lasting for at least two minutes.

5. Our criteria of an abnormal response after exercise are admittedly more inclusive and will be "defended" subsequently. They include: (1) disturbances of cardiac mechanism: (a) appearance of premature beats; (b) increase in frequency of premature beats; (c) tachycardias (atrial flutter or fibrillation, supraventricular or ventricular tachycardia); (2) alterations in conduction: (a) in the A-V node, P-R prolongation, appearance of second or third degree A-V block; (b) bundle branch system block, left, right, or prolonged intraventricular conduction; (3) changes in repolarization of the ventricles: (a) displacement of the S-T (J) junction or S-T segment of 0.5 mm. or more in any lead; (b) change in the QRS-T angle of 25 degrees or more in the horizontal or frontal planes; (c) increase in magnitude of an abnormal T vector; (d) inversion of the U wave.

RESULTS

RHEUMATIC HEART DISEASE

Electrocardiographic changes after the standard two step exercise test, significant according to our criteria, occurred in forty-eight of the ninety-two patients with rheumatic heart disease (52.2 per cent), twenty-five of the forty-two patients receiving digitalis (59.5 per cent), and twenty-three of the fifty patients not receiving digitalis (46 per cent) (Table 1) (Figs. 2–7). Because digitalis itself can produce changes in the ST-T complex after exercise, the responses of the fifty patients not receiving digitalis have been analyzed in greater detail than those of the patients receiving digitalis.

Response to Exercise of Patients not Receiving Digitalis: The standard two step exercise test produced electrocardiographic changes in twenty-five of the fifty patients not receiving

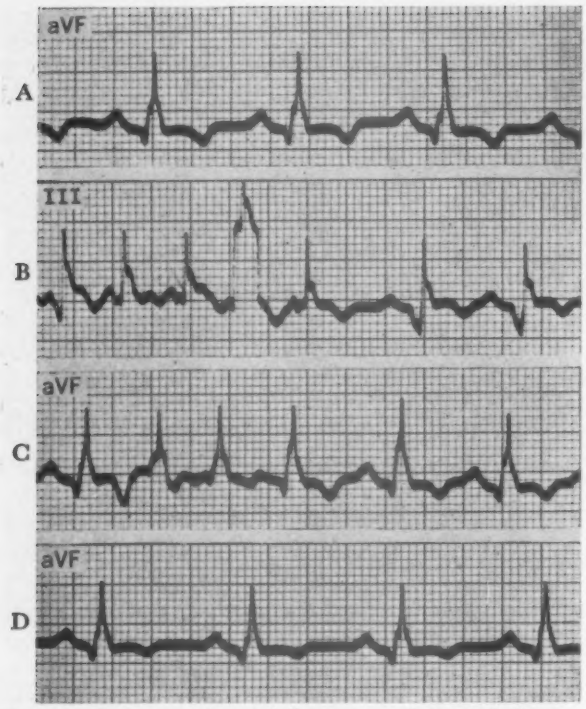


FIG. 4. Paroxysmal atrial flutter, an abnormal electrocardiographic response to exercise of a patient with rheumatic heart disease. The patient (R. C.) was a thirty-six year old man with aortic insufficiency, sinus rhythm, left ventricular hypertrophy, delayed left intraventricular conduction and no evidence of arteriosclerotic heart disease or myocardial infarction. A, control record shows regular sinus rhythm. B and C, segments of records (leads III and aVF) immediately after exercise, show one second paroxysms of atrial flutter or coarse atrial fibrillation which subsided spontaneously within two minutes (D).

digitalis, one change in eighteen, two in five, and three in two patients (Table I).

Transient changes in mechanism occurred after exercise in six patients with two showing premature atrial beats (Fig. 2), two premature ventricular beats (Fig. 3), one supraventricular tachycardia, and one atrial flutter (Fig. 4). Increased displacement of the S-T segment was noted in the atrial premature beats (Fig. 2), and T wave inversion occurred after premature ventricular beats (postextrasystolic) (Fig. 3).

Depression of the S-T (J) junction of at least 0.5 mm. occurred in the electrocardiograms of nine patients. In two instances this was due to a large wave of atrial repolarization and was not considered significant. Otherwise the atrial waves (P, f, F) did not obscure the recognition of S-T displacement (Fig. 5). Depression of both the S-T (J) junction and S-T segment occurred in eleven patients, over 1.0 mm. in seven, between 0.75 and 1.0 mm. in two, and between 0.5 and 0.74 mm. in one patient each.

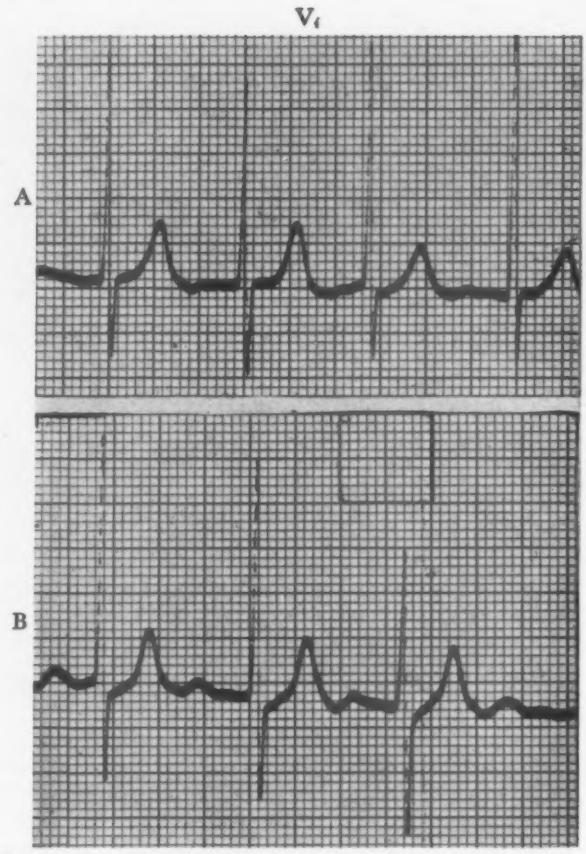


FIG. 5. Abnormal electrocardiographic response to exercise of R. S., a thirty-three year old man with rheumatic heart disease, mitral stenosis and insufficiency, left atrial and left ventricular hypertrophy and atrial fibrillation; functional and therapeutic classification IIB. The patient was not receiving digitalis. A, control record. B, the postexercise electrocardiogram shows more than 1.0 mm. depression of the S-T segment in lead V_4. The presence of atrial fibrillation eliminates the atrial wave of repolarization as the cause of the S-T segment depression.

Changes in the T vector were of two types: (1) a change in the angle between the QRS and T vectors (six patients) and (2) an increase in magnitude of the T vector (two patients). In all subjects with a change in the angle QRS-T, the ventricular gradient[25,26] was calculated and a concomitant change in the angle QRS-G was observed. This is an abnormal response according to Gardberg and Rosen[28] and differs from the change in angle QRS-T secondary to a diminution in the magnitude of the gradient found in certain nonpathologic states (tachycardia, smoking, exercising, eating and taking digitalis). There were two subjects with a change in sign of the T wave in a limb lead (III and aVL) resulting from the movement of the electrical axis of the heart with a secondary shift of the T vector.

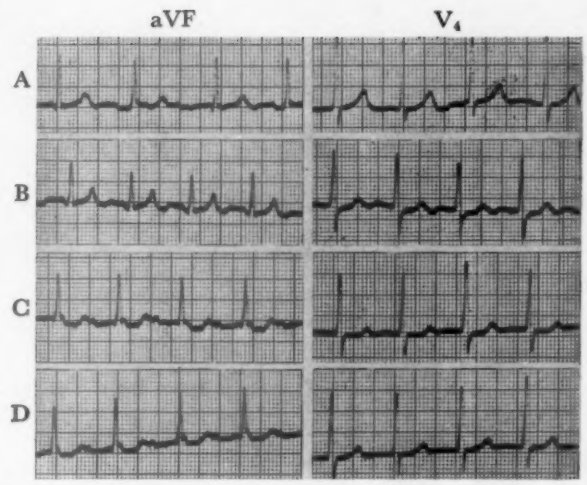


FIG. 6. Abnormal electrocardiographic response to exercise in a patient with rheumatic heart disease and atrial flutter, not receiving digitalis. The patient (A. R.), was a forty-seven year old woman with mitral stenosis and left atrial hypertrophy and dilatation; functional and therapeutic classification, IIB. A, control record shows atrial flutter with varying 3 : 1 and 4 : 1 A-V conduction. B, immediately after exercise there is 2 : 1 A-V conduction and more than 1.0 mm. depression of the S-T segment in V_4. C and D, two and five minutes after exercise show recovery with residual ST-T changes, i.e., flattening of the S-T segment in lead aVF and lower amplitude of the T wave in V_4.

The significant electrocardiographic changes observed in twenty-five of the fifty patients not receiving digitalis were evaluated by five sets of criteria (Table I). There were nine abnormal responses (18 per cent) according to the most restrictive criteria, those of Lepeschkin and Surawicz.[3] As the criteria became more inclusive, more abnormal responses were noted. Thus, according to the criteria of Myers and Talmers[18] eleven (22 per cent) were abnormal; according to Master's revised criteria in 1957[17] twenty (40 per cent) were abnormal; according to his criteria of 1950[16] twenty-three (46 per cent) were abnormal; and twenty-three (46 per cent) were abnormal according to our criteria.

Observations on the Entire Study of Patients with Rheumatic Heart Disease: In an attempt to clarify the causes of an abnormal response to exercise, we have characterized our patients further, as to pre-exercise cardiac rhythm, functional and therapeutic classification,[30] age, sex, valvular lesions, cardiac chamber enlargement and response to the Valsalva maneuver. These were compared with the type of response to exercise (normal or abnormal) according to our criteria.

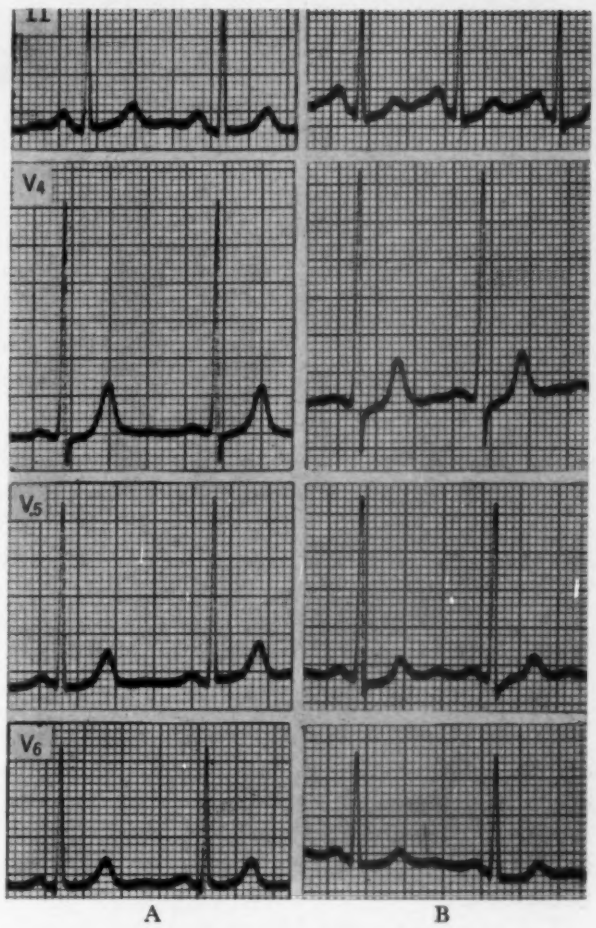


FIG. 7. Abnormal electrocardiographic response to exercise of H. C., a thirty-seven year old woman with rheumatic heart disease, stenosis and insufficiency of the mitral and aortic valves and left atrial and ventricular hypertrophy; therapeutic and functional classification, IIC. A, control record. B, immediately after exercise shows 1.0 mm. depression of the S-T segment in chest leads and increased Ta displacement which deforms the S-T segment in lead II, without significant S-T displacement.

Sinus rhythm was present before exercise in sixty-two subjects, *atrial fibrillation* in twenty-nine subjects, and *atrial flutter* in one subject (Fig. 6). Abnormal electrocardiographic responses to exercise occurred less frequently in subjects with pre-exercise sinus rhythm than in those with atrial arrhythmias (atrial fibrillation, atrial flutter), i.e., 40.3 per cent (twenty-five of sixty-two subjects) and 76.7 per cent (twenty-three of thirty subjects), respectively (Fig. 7). The waves of atrial fibrillation showed an increase in amplitude and a decrease in rate after exercise in ten of twenty-nine patients with atrial fibrillation. Eight of these ten had abnormal responses to the exercise tests for other reasons.

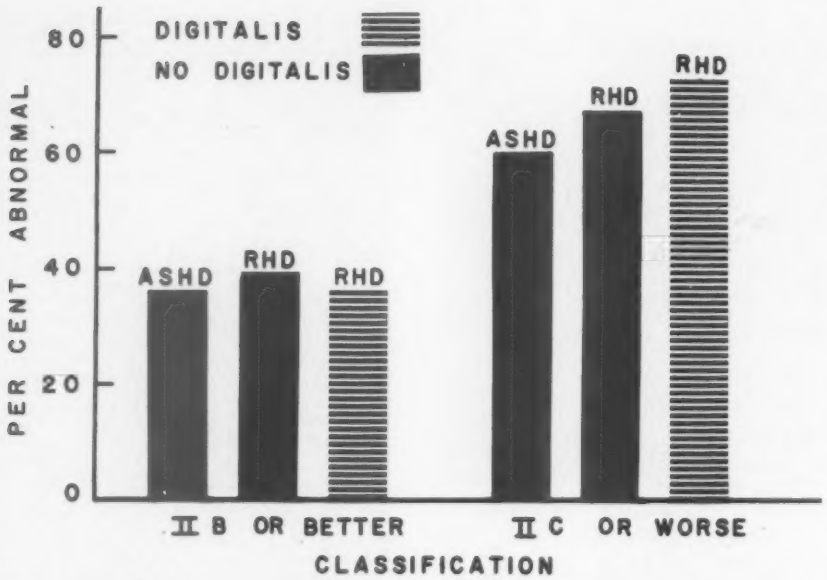


FIG. 8. Relation between the electrocardiographic response to exercise according to our criteria, therapeutic and functional classification and digitalis medication in rheumatic heart disease and arteriosclerotic heart disease with old infarction.

The greater severity of the rheumatic heart disease in patients with an arrhythmia before exercise is indicated by the fact that twenty-seven of twenty-nine patients with atrial fibrillation were receiving digitalis (see following paragraph).

The functional and therapeutic classification[30] was determined by the examining physician, independent of the electrocardiographic data. The functional and therapeutic classification of the patients not receiving digitalis was better than that of the patients receiving digitalis: 76 per cent (thirty-eight of fifty) and 38.1 per cent (sixteen of forty-two), respectively, were classified IIB or better. However, the incidence of abnormal responses was similar for the same classification in the two groups (Fig. 8). Abnormal responses occurred in the IIB or better class in 39.5 per cent (fifteen of thirty-eight) of those not receiving digitalis and in 37.5 per cent (six of sixteen) of those receiving digitalis. Similarly, 73 per cent (nineteen of twenty-six) of those receiving digitalis and 66.7 per cent (eight of twelve) of those not receiving digitalis with classifications of IIC or worse had abnormal electrocardiographic responses to exercise. The greater incidence of abnormal responses in patients receiving digitalis (59.5 per cent) is probably due to the larger number of patients with "worse" classifications rather than to any specific effects of the drug.

Exercise produced symptoms in thirty-four patients, more commonly in the patient receiving digitalis (twenty-four of forty-two subjects) than in patients not receiving digitalis (ten of fifty). Dyspnea was the most common symptom and was mild in nineteen and moderate or severe in twelve subjects. Two patients experienced palpitations. Angina pectoris or its equivalent (substernal fullness or discomfort) occurred in only two subjects. Their response to exercise was considered abnormal because of associated S-T segment displacement.

The predominance of men (76 per cent) is characteristic of the general population of work classification clinics.[8] *The average age* of the entire group was thirty-eight years, of those not receiving digitalis it was thirty-three years, and of those receiving digitalis, forty-two years. The incidence of abnormal responses was similar in patients of all ages not receiving digitalis except for those who were younger than thirty years, i.e., 32 per cent of those less than thirty years, 56.5 per cent of those thirty to forty-nine years, 62.5 per cent of those forty to forty-nine years, and 60 per cent of those fifty years or older. The lower incidence of abnormal responses in the youngest group was related to the functional and therapeutic classification more than to age *per se*. Ten of the twenty patients less than thirty years old and not receiving digitalis had a functional and therapeutic classification of IB or better, five of these being the only patients classified IA,

TABLE II

Incidence of Abnormal Electrocardiographic Responses to Exercise in 100 Subjects with Previous Myocardial Infarcts According to Various Criteria

Electrocardiographic Change	No. of Patients	Criteria					
		Master[16,17]		Myers and Talmers[18]	Lepeschkin and Surawicz[3]	Present Authors	
		1950	1957			Definite	Probable
1. Mechanism (premature beats)	4	4	0	0	0	4	0
2. S-T segment							
(1) Depression of the S-T (J) junction 0.5 to 0.74 mm.	3	3	3	0	0	3	0
(2) Depression of the S-T segment:							
(a) 0.5 to 0.74 mm.	4	4	4	4	0	4	0
(b) 0.75 to 1.0 mm.	1	1	1	1	1	1	0
(c) more than 1.0 mm.	6	6	6	6	6	6	0
3. Change of 25 degrees or more in the QRS-T angle							
(1) With definite change of sign of a T wave in any lead	6	4*	5*	3	1	6	0
(2) Without definite change of sign of T wave in any lead	7	0	0	0	0	5	2
4. Increase in magnitude of an abnormal T vector	3	0	0	0	0	0	3
5. 2 and 4	3	3	3	3	3	3	0
6. 2 and 3	4	4	4	4	4	4	0
7. 2 and 1	2	2	2	2	2	2	0
8. 1 and 3	2	2	0	0	0	2	0
9. 1 and 4	2	2	0	0	0	2	0
10. Conduction defect (left bundle branch block) 1 and 2	1	1	1	1	1	1	0
Total no. and per cent	48	36	29	24	18	43	5

* Differences in Master's figures in 1950 and 1957 are because of different lead selection.

whereas only one of the seven patients fifty years or over not receiving digitalis was classified IB or better. The greater incidence of abnormal responses in the older patients (above thirty years) was considered more likely due to the longer duration of rheumatic disease and a poorer functional and therapeutic classification rather than to age *per se* or the development of coronary atherosclerosis.

The incidence of abnormal responses was unrelated to a specific valve or to the number of valves involved. Abnormal responses occurred in 52.8 per cent (nineteen of thirty-six) of patients with mitral valvular disease, in 54.4 per cent (twenty-four of forty-four) of patients with mitral and aortic involvement, and in four of ten patients with only aortic involvement. However, in general the incidence of abnormal responses increased with the number of hypertrophied chambers, i.e., with more severe disease. Twelve of fifteen patients (80 per cent) with hypertrophy of three chambers (both ventricles and left atrium) had abnormal responses while only three of twelve patients (25 per cent) of those with no chamber hypertrophy responded abnormally.

Flack Test: There were forty-one abnormal responses in the eighty patients who performed the Valsalva maneuver, 44.5 per cent (twenty of forty-four) in patients not receiving digitalis and 58.3 per cent (twenty-one of thirty-six) in patients receiving digitalis. The response to the Valsalva maneuver correlated with the electrocardiographic response to exercise: 65.9 per cent (twenty-seven of forty-one) with an abnormal response to the Flack test had an abnormal electrocardiographic response to exercise and 64 per cent (twenty-five of thirty-nine) with a normal response to the Flack test had a normal electrocardiographic response to exercise.

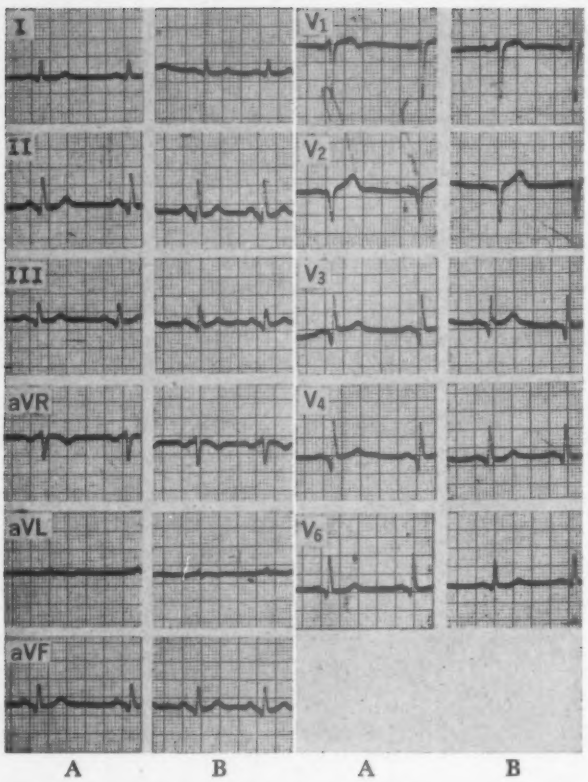


FIG. 9. Normal electrocardiographic response of J. R., a sixty year old man, with anterior and posterior myocardial infarcts. A, control. B, immediately after exercise.

ARTERIOSCLEROTIC HEART DISEASE WITH PREVIOUS MYOCARDIAL INFARCTION

Types of Electrocardiographic Response: The various types of changes in the electrocardiograms after exercise in the 100 subjects with previous myocardial infarction are presented in Table II and in Figures 9 to 16. In forty-eight of the 100 subjects, sixty-three significant electrocardiographic changes occurred, one in thirty-four subjects, two in thirteen subjects, and three in one subject. Twenty-four subjects showed depression of the S-T segment or the S-T (J) junction of 0.5 mm. or more either alone or in combination with other changes. Three showed depression of the S-T junction only, with an immediate ascent of the segment to the baseline and into the ascending limb of the T wave in the absence of significant tachycardia (110) or descent of the Ta (P-R) segment. These changes were considered significant by our criteria and those of Master. Four other subjects showed depression of the S-T (J) junction and S-T segment greater than 0.5 mm. and less than 0.75 mm. and in addition were considered abnormal by the criteria of Myers and Talmers. Of the remaining seventeen subjects, two showed depression of the S-T (J) junction of more than 0.75 mm. and less than 1.0 mm., and fifteen showed greater than 1.0 mm. depression of the S-T (J) junction and S-T segment and were considered abnormal by all criteria (Fig. 11) (Table II).

T Wave Changes: There were two types of significant changes in the T vector: (1) change in the angle between the mean QRS and T vectors and (2) an increase in the spatial magnitude of an abnormal T vector, i.e., an abnormal T wave becoming more abnormal or more deeply inverted. There were nineteen instances in which a change in the angle QRS-T of 25 degrees or more occurred alone or in combination with other changes in the electrocardiogram. The change in the angle between the mean QRS and mean T vectors resulted from a change in position of the mean QRS vector, the mean T vector or both. Because of the frequent rightward movement of the QRS axis in the frontal plane after exercise (occurring in forty-six of our patients), it was important to evaluate the position of the mean QRS vector before deciding whether significant T wave changes had occurred. Inversion of the T wave in a particular lead was commonly due to the movement of the mean QRS and mean T vector to the right without a change in the angle between them. Conversely, in eleven of the nineteen cases a change in the QRS-T angle was due to predominant movement of the mean QRS vector, but not of the T vector. The failure to detect QRS-T angle changes by the conventional pattern analysis and failure to record twelve leads after exercise account for some of the difference in interpretation of T wave abnormalities by various criteria (Table II).

In all cases in which a significant change in the QRS-T angle occurred, the ventricular gradient was also calculated.[25–27] The angle between the ventricular gradient and the QRS was found to change in each case as mentioned previously. Gardberg and Rosen[28] have suggested that there are a variety of nonpathologic factors that diminish the magnitude of the ventricular gradient, producing changes in the QRS-T angle which are secondary to this nonpathologic diminution in the gradient. Primary changes in the angle between the QRS-T, they state, are associated with changes in the angle between the mean QRS and G. All of

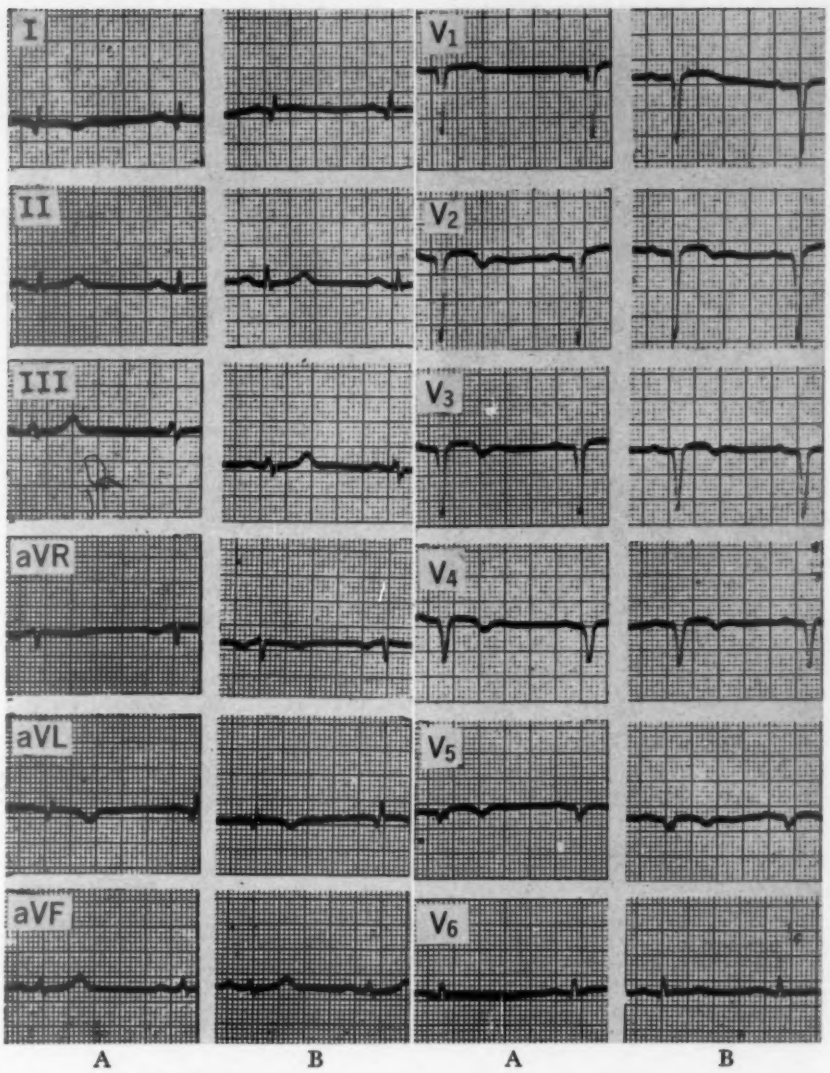


FIG. 10. A normal electrocardiographic response to exercise in A. K., a fifty-eight year old man with an old anteroseptal myocardial infarction and a ventricular aneurysm. A, control. B, immediately after exercise.

our subjects with a significant change in the angle QRS-T had an associated change in the angle QRS-G which represented, according to these criteria, primary T vector changes.

The second type of T vector change noted was an increase in the spatial magnitude of an abnormal T wave. This change occurred in eight subjects, singly in three and in combination with other abnormal changes in five (Table II). We classified this change as being "probably abnormal" because the T vector normally decreases in magnitude after the single standard two step exercise test.[3,31]

U Wave Changes: The magnitude of the U wave increased in the precordial leads of eight subjects and decreased in one. These changes are considered normal, having been reported in normal subjects after exercise.[31] Inversion of the U wave after exercise is an abnormal finding[3,31,32] but did not occur in the present series. The U wave changes were not invariably dependent on ST-T changes. Of these nine subjects with U wave changes, only four showed ST-T changes (three had depression of the S-T segment of over 1.0 mm., and one, change in the QRS-T angle); in one, premature ventricular beats developed; and four showed no other change.

Table II is a comparison of the incidence of abnormal responses to exercise according to the five sets of electrocardiographic criteria. As the criteria become more inclusive, the number of abnormal responses increases. Thus, there were eighteen abnormal responses ac-

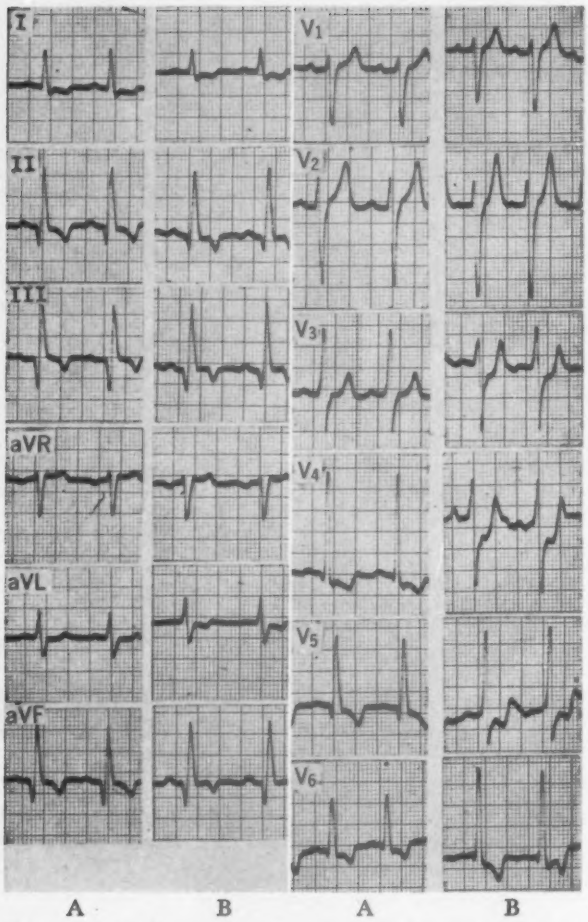


FIG. 11. An abnormal response to exercise according to all criteria (2.5 mm. S-T segment depression) in J. E., a forty-eight year old man with an old posterolateral myocardial infarct. A, control. B, immediately after exercise.

cording to the most restrictive criteria (Lepeschkin's and Surawicz'), twenty-four abnormal responses according to the criteria of Myers and Talmers, twenty-nine abnormal responses as judged by the revised criteria of Master in 1957, thirty-six abnormal responses as judged by the criteria of Master in 1950, and forty-three abnormal and five probably abnormal responses according to our admittedly more inclusive criteria.

Clinical Correlations: The electrocardiographic response to exercise has been correlated with other factors: (1) functional and therapeutic classification, (2) symptoms of coronary insufficiency, (3) age, (4) type of residual electrocardiographic change of infarction in the control record and (5) location of the infarction.

1. Abnormal responses occurred more commonly in the more severe cases as judged by the New York Heart Classifications:[30] in 36 per cent (eighteen of fifty) with functional and therapeutic classifications of IB or IIB, and in 60 per cent (thirty of fifty) of IIC or IIIC. This difference is statistically significant, $p = <0.05$.

2. Symptoms of coronary insufficiency (angina pectoris or its equivalent) occurred during the test in twelve of forty-eight patients with abnormal electrocardiographic responses according to our criteria and in only four of fifty-two with normal electrocardiographic responses to exercise, $p = <0.05$.

3. There was an equal incidence of abnormal responses to exercise in patients of all ages. The average age of the entire group was fifty-one years.

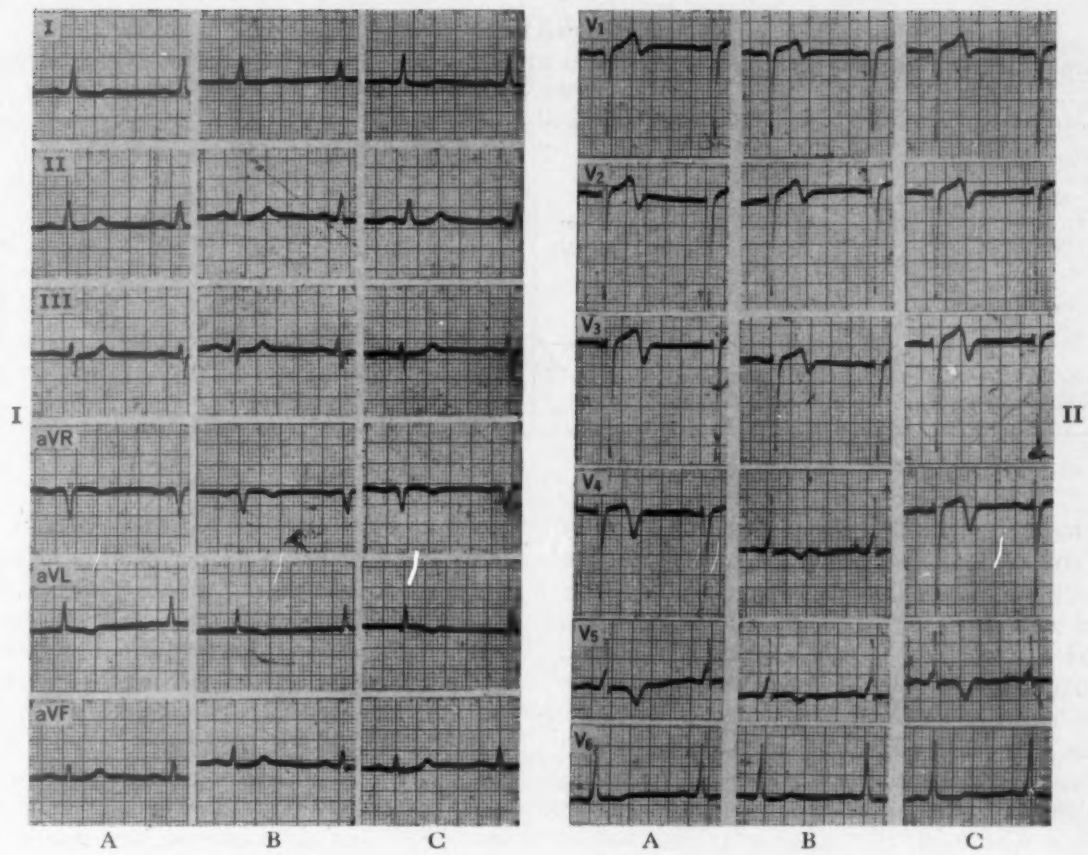
4. The type of residual electrocardiographic change of infarction in the control record (QRS, ST-T, QRS and ST-T, or none) was unrelated to the electrocardiographic response to exercise.

5. Abnormal electrocardiographic responses occurred more frequently in patients with old anterior (septal and lateral) infarcts than in patients with old posterior (inferior) infarcts; 64.4 and 35.7 per cent, respectively, $p = <0.05$.

COMMENTS

The electrocardiographic criteria for an abnormal response to the two step exercise test are still in dispute with various criteria being proposed to distinguish the false-positive responses from those due to coronary artery disease.[3] In general the validity of the interpretations has rested on the presence, absence or subsequent clinical development of coronary artery disease in the patients studied.[3,17,22] More recently the assumption has been made that relative or absolute ischemia of the myocardium is the sole cause of electrical changes after exercise.[12]

The incidence of abnormal responses in our series of patients with rheumatic heart disease was substantial with each of the five sets of electrocardiographic criteria employed and was approximately the same, according to each set of criteria, in rheumatic heart disease and in arteriosclerotic heart disease with myocardial infarction (Table III). Not only did the less inclusive (more restrictive) criteria fail to distinguish between coronary atherosclerosis and rheumatic heart disease, but also they failed to identify patients in both groups with less severe forms of heart disease. According to



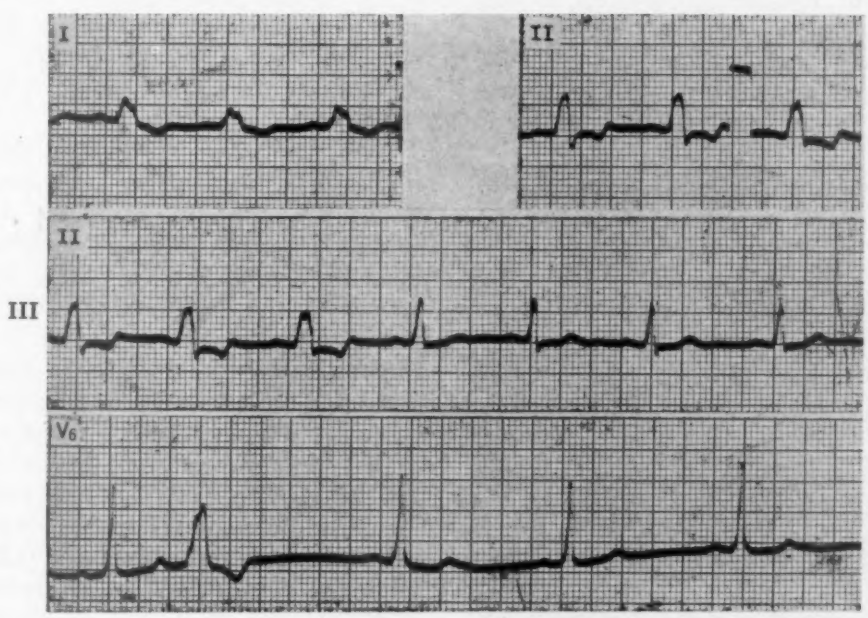


FIG. 12. Transient left bundle branch block, an unusual electrocardiographic response to exercise of J. L., a fifty-seven year old man with an old anteroseptal myocardial infarct and incomplete left bundle branch block. In parts I and II, A is the control record. In part III, leads I and II immediately after exercise show transient left bundle branch block. B, recorded immediately after part III shows increased negativity of the U wave in V_4 and V_5. C, five minutes later showing recovery.

TABLE III

Abnormal Electrocardiographic Response to Exercise in Rheumatic and Arteriosclerotic Heart Disease as Judged by Various Criteria

Heart Disease	No. of Patients	Criteria				
		Master[16,17]		Myers and Talmers[18] (%)	Lepeschkin and Surawicz[8] (%)	Ours (%)
		1950 (%)	1957 (%)			
Rheumatic*	50	46	40	22	18	46
Arteriosclerotic with old myocardial infarction*	100	36	29	24	18	48

* Not receiving digitalis.

our more inclusive criteria, the incidence of abnormal responses varied according to the severity of disease as measured by the functional and therapeutic classification, regardless of the cause (Fig. 8). A similar relationship for patients with mitral stenosis has been recently reported by Ramsey and Beeble.[12]

The possibility must be raised that occult coronary disease was responsible for the comparable incidence of abnormal responses in patients with both the rheumatic and arteriosclerotic heart disease. Although it is likely that a significant number of patients in our study had morphologic coronary lesions[33] (as does a large percentage of American adults[34]), clinical evidence of coronary atherosclerosis or insufficiency in our patients with rheumatic heart disease was conspicuously absent. Specifically, none had a history of or electrocardiographic evidence of myocardial infarction. In only two of ninety-two patients was substernal discomfort elicited by the performance of the two step test. The occurrence of dyspnea during exercise in thirty-four patients admittedly could be construed as an anginal equivalent rather than an indication of myocardial insufficiency. This lack of conventional symptoms and signs of coronary atherosclerosis and insufficiency plus the comparable incidence of abnormal responses in patients of all ages with like severity of disease would tend to eliminate occult significant coronary atherosclerosis as the major cause of the abnormal responses in the present study.

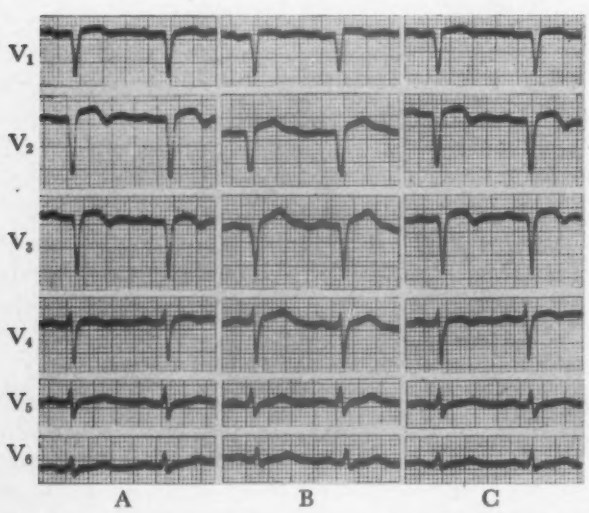


FIG. 13. An abnormal response to exercise of E. B., a sixty-three year old woman with an old anteroseptal myocardial infarction. A, control record. B, immediately after exercise. The T waves in leads V_2 to V_4 become upright and appear "normal." C, five minutes after exercise, return to the control.

How, then, can one explain the remarkable similarity of the incidence and types of abnormal electrocardiographic responses in two dissimilar etiologic groups? Spurious S-T displacement produced by Ta changes was excluded by the design of our study.[3,18,31] It is unlikely that hyperventilation *per se* was an important factor, since only twelve patients with rheumatic heart disease experienced undue dyspnea after exercise. Furthermore, since hyperventilation may produce T wave changes but no significant S-T displacement,[35] hyperventilation cannot account for the similar incidence of abnormal responses found in both etiologic groups when judged according to criteria which exclude or minimize the importance of T wave changes.

Similarly, the effect of digitalis has been excluded as a causative factor by the selection of patients not taking digitalis, and furthermore, probably can be absolved even in patients receiving digitalis since the incidence of abnor-

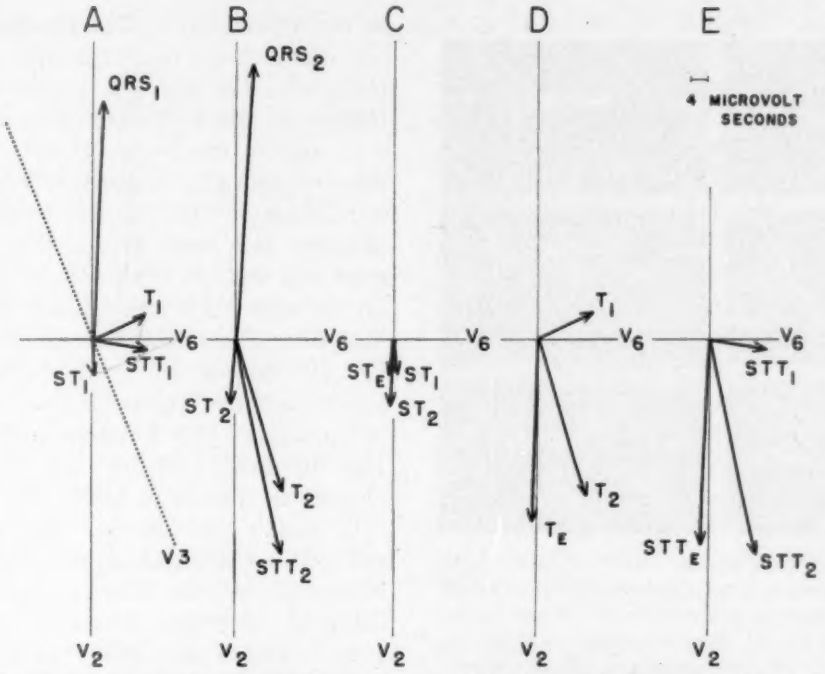


FIG. 14. Same patient as in Figure 13. A, the horizontal plane projections of the mean QRS, S-T, T and ST-T vectors of the control electrocardiogram are calculated from precordial leads V_3 and V_6 and are shown as in Figure 13. B, the same calculations are made for the QRS, S-T, T and ST-T vectors immediately after exercise. C, D and E, the effective S-T, T and ST-T vectors of exercise ($S\text{-}T_E$, T_E, $ST\text{-}T_E$) are calculated by subtracting the vectors before exercise ($S\text{-}T_1$, T_1, $ST\text{-}T_1$) from the vectors after exercise ($S\text{-}T_2$, T_2, $ST\text{-}T_2$). The effective S-T, T and ST-T vectors of exercise point toward the area of infarction.

mal electrocardiographic changes was similar in rheumatic and arteriosclerotic patients not receiving digitalis, and in digitalized patients with rheumatic heart disease with comparable therapeutic and functional classifications (Fig. 9).

Factors Causing Positive Exercise Tests: The factor common to patients with rheumatic heart disease with abnormal electrocardiographic responses was the relative inadequacy of the mechanical (pumping) function of the heart. The patient with the poorer functional and therapeutic classifications, with a greater number of enlarged cardiac chambers, and with abnormal Valsalva (Flack) tests were most likely to have abnormal electrical responses.

An obvious common feature of the response to exercise of the patients with arteriosclerotic and rheumatic heart disease was the failure to increase cardiac output adequately during exercise.[24,36] In the former this failure was most likely due to myocardial inadequacy associated with mechanical valvular dysfunction, and in the latter, due to myocardial inadequacy secondary to inadequate coronary inflow through a narrowed coronary bed. The ultimate physiologic effects may be quite similar: (1) incurrence of a large oxygen debt;[7] (2) failure to increase the supply of blood to the tissues; (3) relative deficiency of coronary perfusion due to (a) failure to increase systemic arterial blood pressure (coronary perfusion pressure),[24] (b) disproportionate increase of heart rate with concomitant reduction of time in diastole available for coronary flow, and, particularly significant in rheumatic heart disease, for ventricular filling, (c) stretching of the atrial and ventricular myocardium due to altered hemodynamics with retarded coronary inflow and retrograde collateral flow;[37] and (4) variable effects on rhythmicity, contractility and repolarization of the myocardium produced by the aforementioned, by sympathetic and other nervous stimulation and emotions.[38]

The postexercise electrocardiographic changes in patients with rheumatic and arteriosclerotic heart disease thus represent alterations in the myocardial membrane and function produced by an interreaction of many factors: changes in coronary perfusion, in valvular function and cardiac mechanism. Modification of these

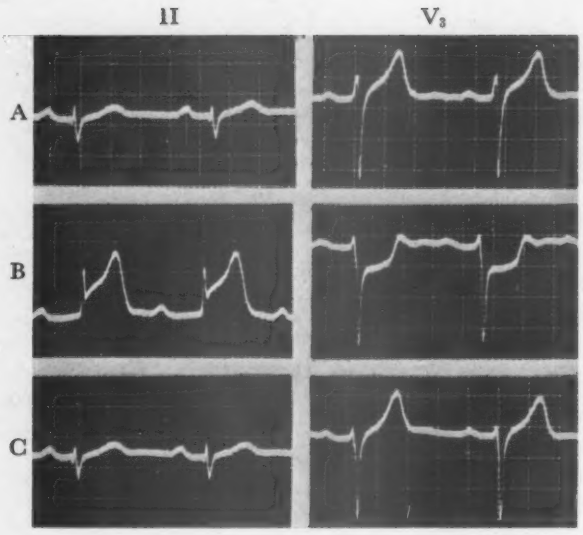


FIG. 15. Transient monophasic curves of acute myocardial ischemia occurring after the performance of the two step exercise test by patient E. M., a forty-seven year old man with an old posterior myocardial infarct. A, control record. B, immediately after exercise, monophasic curves of ischemia and first degree A-V block appear. C, return to normal within five minutes. An acute posterolateral infarct developed fourteen months after this exercise test.

factors, whether by surgery, drugs or physical training programs,[14] often enables the patient with rheumatic or arteriosclerotic heart disease later to perform the two step test and other activities without abnormal electrocardiographic changes.

Clinical Significance of Positive Exercise Test: Since the response to the two step exercise test is abnormal in less than half the patients with known chronic valvular rheumatic heart disease or previous myocardial infarcts, and since in many subjects without clinical evidence of organic heart disease (neurocirculatory asthenia,[39] disorders of the heart beat,[13] and physical unfitness[14]) electrocardiographic changes develop after exercise similar quantitatively and qualitatively to those of patients with coronary artery disease and insufficiency, it would seem that electrocardiographic changes after the exercise test *per se* are of little diagnostic importance, i.e., are not specific for etiology.

In our opinion the results of the exercise test should be used as an adjunct with other clinical data to assess circulatory fitness. In this frame of reference, the exercise test becomes more meaningful if analyzed in greater rather than lesser detail. The importance of the influence of the atrial T wave[3,18] and its influence on the S-T junction and even the S-T segment should be re-emphasized.[3] The changes in the T wave are more easily understood, and important T wave changes are less likely to be missed if related to the QRS complex. Our view that a change in the angle QRS-T of 25 degrees or more signifies an abnormal response has been reinforced by the finding that in all of our subjects with such a change there was a concomitant change in the angle QRS-G. This is an abnormal response according to Gardberg and Rosen[28] and differs from the widened angle QRS-T found in nonpathologic states. As mentioned previously, the nonpathologic change in the angle QRS-T is associated with a diminution in magnitude of the gradient with no change in the angle QRS-G.

T Vectors after Exercise: In cases in which the control electrocardiogram is abnormal the effects of exercise may be more readily recognized if they are portrayed vectorially. We have determined the "effective vector" of exercise in the patients with old myocardial infarcts by subtracting the T vector before exercise from the T vector after exercise according to a method employed previously.[29] The T vector after exercise is the resultant of two forces, the resting T vector and the "effective T vector of exercise." In the electrocardiograms of eleven of thirteen patients with anterior or posterior infarcts that showed significant change only in the QRS-T angle, the calculated effective vector of exercise pointed toward the area of the old infarct. This effect of exercise tends to neutralize the abnormal T vector which in the control record points away from the area of infarction and to make the T wave appear more "normal" (Figs. 13 and 14). The neutralization of the abnormal T vector of infarction may be the result of ischemia of the subepicardial layers of the opposite wall of the heart or more likely of ischemia of the subendocardial layers of the previously infarcted area. The addition of the two abnormal T vectors, the T vector of infarction and the T vector of the area of ischemia after exercise, cancels and produces a more "normal" appearing T wave.[29]

Conduction Defects: The appearance of abnormalities of A-V or intraventricular conduction (bundle branch system block) (Fig. 12) or ectopic activity after exercise has been considered abnormal by some[16,31] but not by other criteria.[3,17,18] In our opinion such responses should be considered abnormal because these abnormalities do not develop in normal sub-

jects and trained athletes during and after exercise,[18] and because of the ominous significance of heterotopic activity and disorders of conduction appearing in subjects with heart disease.

Valsalva Maneuver: The correlation of abnormal responses to the two step test and the Valsalva maneuver is interesting because the former is dynamic, requiring substantial peak expenditure of energy, and the latter is static and insignificantly calorigenic. In both tests a stress is imposed upon the circulation, the response to which reflects a measure of myocardial competence.[19]

Gorlin, Knowles and Storey[19] have noted that abnormal responses to the Valsalva maneuver may occur in incipient or overt right or left ventricular failure, and in tightly stenotic valvular lesions. An abnormal response can be explained in terms of modified Starling curves of ventricular function.[40] An abnormal response to the Valsalva maneuver implies that a decrease in filling pressure failed to affect stroke work and output. This occurs in the high ranges of filling pressures (as in tight valvular stenosis) or on a flat ventricular function curve. Sarnoff, Berglund and Case[40,41] have demonstrated "that constriction of the coronary artery, resistance to ventricular outflow, anemia and many other factors can alter the slope of the work filling pressure curve in a given animal." Thus, various types of heart disease in man can produce similar flat ventricular function curves. In such cases the Valsalva maneuver will not diminish cardiac output significantly, there will be no autonomic reaction,[21] and the normal blood pressure and pulse rate response will not occur.

Like the electrocardiographic response to the two step test,* the response to the Valsalva maneuver is not specific for etiology. The high prevalence of abnormal responses in our series indicates that subclinical failure or decreased myocardial reserve was present in many of our patients. The diminution of the ventricular gradient in congestive failure[28] and the influence of the gradient on the S-T segment[27] would suggest the possibility that associated with the altered ventricular function curve and myocardial myosin metabolism[42] is an alteration in the ability of the myocardial cell to maintain its intra- and extracellular sodium and potassium gradients under stress. This possibility could help to explain some of the correlations of contractile and electrical functions noted in our results.

Exercise Test as Measure of Circulatory Fitness: The two step exercise test has proved to be of greater value in our experience as an objective measure of circulatory fitness for brief peak exercise than in establishing an etiologic diagnosis. The value of the test has been enhanced by observations on pulse rate and blood pressure in addition to changes in the "electrical parameter."[7] The standard two step test has been shown to have a sound physiologic basis in demanding an equal energy requirement in all subjects regardless of age, height or weight.[7] The amount of energy required is 8.5 calories per minute, roughly comparable to climbing and descending two flights of stairs or walking at 4.8 miles per hour. The rate of work performed in the two step test is greater than the peak performances required in most industrial occupations including the factory,[43] steel mill[44] and the docks.[45] It is of practical importance that, like the two step test, peak efforts of most jobs are usually sustained for brief periods of time of less than two minutes.[45]

The response of the two step test, when related to other medical, vocational, social and psychiatric data,[6] has been valuable in prescribing daily activities and work for subjects with heart disease. Using these methods we have been able to return 80 per cent of the first 1,000 patients seen at the Work Classification Clinic of The Cleveland Area Heart Society to productive employment commensurate with their functional and therapeutic limitations.[8]

Possible Dangers of Test: The hazard of subjecting patients with cardiac disease to the peak effort of the two step test has been negligible in our experience at the Work Classification Clinic with 1,700 patients, 900 of whom have had previous myocardial infarction. Close adherence to the contraindications listed previously and close supervision of the test with a physician in attendance may account for the remarkable fact that there have been no instances of death, precipitation of acute myocardial infarction or congestive failure as a result of the exercise test. In one remarkable instance, in which an associate of the Work Classification Clinic had decided that an exercise test should *not* be

* In our experience the electrocardiographic response to the double standard two step test[22] is similarly not specific. Abnormal responses have been obtained in all etiologic categories, including youngsters with congenital heart disease.

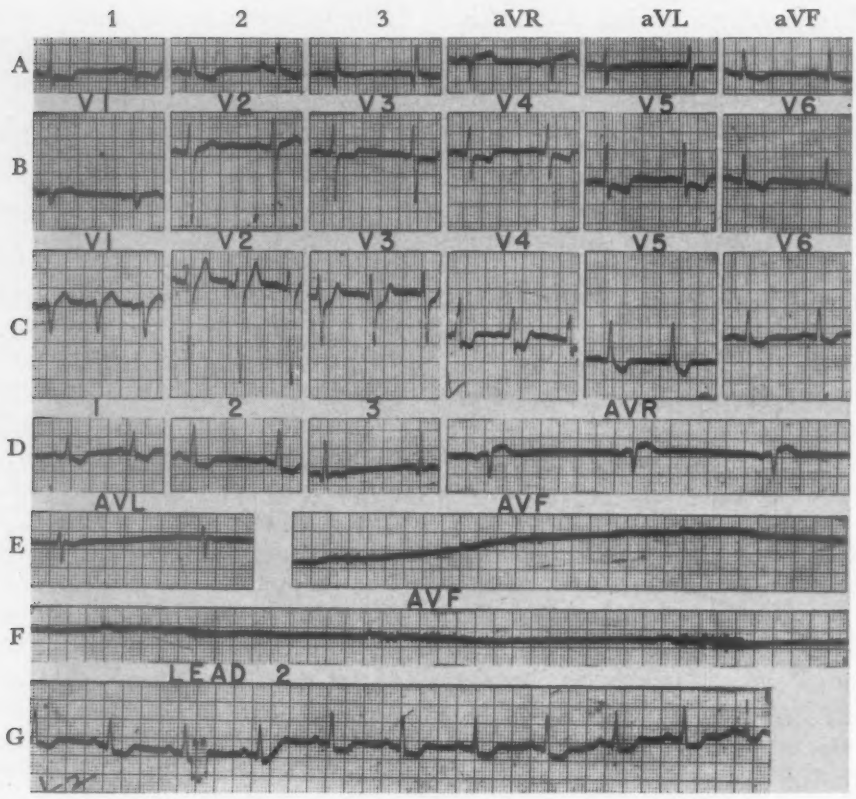


FIG. 16. Transient cardiac arrest occurring after exercise in patient J. G., a thirty-three year old man with an old posterior myocardial infarct. A and B, control record. C, D, E and F, continuous records for the first two minutes after exercise. The sinus pacemaker gradually slowed (D and E) and complete atrial and ventricular standstill occurred suddenly (E and F). G, recovery after seventy-five seconds.

performed, the patient died suddenly several hours after the clinic visit. However, three unusual and noteworthy responses to exercise have been encountered elsewhere in the past nine years. In one subject typical monophasic curves of acute myocardial ischemia developed after exercise. These atypical electrocardiographic changes of angina pectoris[46] reverted to normal within the next minute (Fig. 15). In another subject cardiac arrest developed which lasted for seventy-five seconds after which normal rhythm was restored spontaneously (Fig. 16). The third subject experienced a single episode of ventricular tachycardia following exercise which subsided spontaneously after two minutes of rest.

SUMMARY

1. The electrocardiographic responses of ninety-two consecutive patients with rheumatic heart disease and 100 consecutive patients with arteriosclerotic heart disease who performed a standard two step Master exercise test were analyzed for changes in mechanism, conduction and repolarization and evaluated by five sets of criteria.

2. The incidence of abnormal responses according to the various criteria ranged from 18 to 48 per cent. However, there was no significant difference in the incidence or types of abnormal electrocardiographic responses to exercise in rheumatic or arteriosclerotic heart disease when compared with the same criteria.

3. The incidence of abnormal responses varied according to the severity of disease as measured by the functional and therapeutic classification, regardless of the cause. The incidence of abnormal responses of patients with rheumatic heart disease was not related to age, type of valvular lesion or digitalis medication, but was directly related to the functional status of the heart as determined by the therapeutic and functional classification, cardiac chamber enlargement, presence of atrial fibrillation and electrocardiographic response to the Valsalva maneuver. Abnormal electrocardiographic responses also occurred more commonly in patients with anterior myocardial infarction.

4. We challenge the belief that abnormal electrocardiographic changes occurring after exercise are either diagnostic of coronary arteriosclerosis or caused solely by an insufficient blood supply to the myocardium. Reasons are presented why the interreaction of many facets of myocardial function should be considered in the understanding of the changes produced by exercise.

5. The two step exercise test is a valuable test of cardiac function but is not specific for the diagnosis of cause. The test has proved to be of value as an objective measure of circulatory fitness for brief peak exercise and has been useful for prescribing work and daily activities for patients with all types of heart disease.

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Historical Milestones

Right-Sided Ulcerative Endocarditis Recognized Ante Mortem

(Charcot and Vulpian, 1862)

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CASES of bacterial endocarditis are an unfailing focus of interest in the medical service of any hospital. While in most instances the diagnosis is now made with relative ease and is usually confirmed by the bacteriologist, the intern who first recognizes the illness in a newly admitted patient is the recipient of his colleagues' compliments. The efficiency of modern clinical diagnosis of bacterial endocarditis is the result of a long historical development, the roots of which are distinctly traceable as far back as Laennec's work on auscultation and Virchow's studies of embolism. The case report by Charcot and Vulpian, which is reprinted herein, demonstrates that even the uncommon right-sided form of ulcerative endocarditis could be diagnosed correctly in the pre-bacteriological era. Apart from this interesting historical fact, not well known, the simplicity and ingenuity of the clinical reasoning in the present case commend themselves strongly to the modern physician.

Jean-Martin Charcot (1825–1893) is usually thought of nowadays as the neurologist and dramatic clinical teacher who worked at the Salpêtrière in Paris and made important contributions to the nosography of hysteria, tabes and the muscular dystrophies. It is less often remembered that he also wrote on renal disease, heart disease, tuberculosis, pneumonia and on the chronic diseases of old age.

Edme-Félix-Alfred Vulpian (1826–1887) interned with Charcot at La Pitié and frequently collaborated with him over a period of thirty-seven years. Vulpian was both a noted experimental physiologist and a distinguished clinician. His principal contributions dealt with the experimental physiology of the nervous system including especially the cranial nerves and the vasomotor apparatus. His obituary, written by Charcot, is a model of literary composition.

The article reprinted herewith is titled "Note sur l'endocardite ulcéreuse aiguë à forme typhoïde, à propos d'un cas d'affection ulcéreuse de la valvule tricuspide, avec état typhoïde et formation d'abcès multiples dans les deux poumons." (Note on the typhoidal form of acute ulcerative endocarditis; a case of ulcerative disease of the tricuspid valve with typhoidal state and multiple abscesses in the two lungs.) The text was originally published in the Comptes Rendus des Séances et Mémoires de la Société de Biologie, third series, volume 3 (1861), pages 205 to 221, 1862.

* * *

CHARCOT AND VULPIAN ON ULCERATIVE DISEASE OF THE TRICUSPID VALVE

One of the forms of acute ulcerative endocarditis[1] is noteworthy in that it is accompanied by a group of symptoms which resemble those seen in the typhoidal fevers or in purulent infection and which apparently are connected with profound septicemia. This especially severe kind of endocarditis[2] has been studied especially in foreign countries, particularly by

[1] A brief summary of the present case has been included in the inaugural thesis of Dr. Benjamin Ball (Des embolies pulmonaires, Paris, 1862, p. 118).

[2] This form seems to be the same as the *endocardite gangréneuse* of Bouillaud. See his *Traité des maladies du coeur*, vol. 2, pp. 29–87.

Virchow,[3] Rokitansky,[4] S. Kirkes[5] and O. Beckmann.[6] Quite recently, in two classic treatises on heart disease, Bamberger[7] and Friedreich[8] have summarized the main characteristics. Nevertheless the subject has been incompletely investigated and has not attracted the attention which its clinical importance deserves. Hence we consider it useful to report a case which we have recently encountered and which evidently belongs to the same class of phenomena, at least in essential details.

In the cases under discussion the ulcerations have almost always been found in the left heart and usually are situated on the valves. They are the result of a breakdown or rapid disintegration of the internal membrane of the heart. This is how, according to the most recent investigations[9] this morbid result is attained: the components of the endocardium—plasma cells and intermediate tissue—at first appear infiltrated with an exudative product over a varying distance. They become distended and swollen, then they soften, become dissociated and finally are converted into pultaceous detritus, which under the microscope appears opaque and finely grained and is almost completely resistant to the action of strong reagents, mineral acids or concentrated alkali, and consequently possesses important microchemical characteristics.

This kind of molecular destruction breaks down the affected tissue into thin fragments which become detached one after another and are carried away by the blood current. Thus defects are produced which vary in location, shape, extensiveness, size and depth; and in consequence vascular obstructions occur which are more or less serious and almost always irreparable. If the ulceration is peripheral the valves are detached by their attached margins and become floating or they become shortened by the erosion of their free margins. If the ulceration is central they perforate or become attenuated. In the latter event they can become the origin of the curious lesions which Thurnam,[10] Ecker[11] and Rokitansky[12] have studied under the name of aneurysms of valves. The parts of the endocardium ulcerated in the manner just described can become covered by concretions and fibrinous vegetations. This process of acute ulceration can be primary or can develop on valves which were previously the site of subacute or chronic disease.

These cardiac changes can exist in all forms of ulcerative endocarditis and ordinarily are accompanied by scattered focal lesions in various parts of the body.[13] Most often these are infarcts of the spleen, the kidneys, or the liver, rarely genuine abscesses, certain kinds of cerebral softening and certain rapidly evolving ocular inflammations;[14] circumscribed or diffuse gangrene; or ecchymotic plaques occupying the thickness of the skin, the serous membranes and mucosae, or even located in the depths of the viscera. Nowadays it is generally recognized that these multiple lesions are caused by fragments detached from the endocardial ulcerations and lodged in the ultimate branches of the arterial system (capillary embolism). In the cases under discussion, the centers of infarcts or of ecchymotic plaques have repeatedly been shown to contain arterioles distended and obliterated by accumulations of an amorphous finely grained, opaque material, resistant to reagents and hence similar in all respects to the detritus which comes from acute softening of the endocardium.[15]

That which more especially characterizes the typhoidal form of ulcerative endocarditis is the collection of serious symptoms which appear during the course of the disease, during the very

[3] Virchow, *Ueber Capillaere, Archiv für path. anatom.*, vol. 9, part 2, 1856, p. 307; *Gesamm. Abhandlungen*, 1856, p. 711; *Monatschrift für Geburtskunde*, vol. 11, p. 409, 1858.

[4] Rokitansky, *Pathol. Anatom.*, Wien, 1856, vol. 2, p. 273 and vol. 1, pp. 382 and 380.

[5] S. Kirkes, *Edinb. Medical and Surgical Journal*, vol. 18, p. 119, 1853 and *Archives de médicine*, vol. 1, p. 305, 1853.

[6] O. Beckmann, *Virchow's Archiv*, vol. 12, part 1, 1857, p. 59, and vol. 20, parts 3 and 4, p. 217, 1860.

[7] Bamberger, *Lehrbuch der Krankheiten des Herzens.* Wien, 1857, pp. 164 and 165.

[8] Freidreich, *Die Krankheiten des Herzens. Virchows Handbuch*, vol. 5, part 2, second half, pp. 323 and 328, 1861.

[9] Virchow, *loc. cit.* and *Cellulär Pathologie*, Berlin, 1858, p. 186; O. Beckmann, *loc. cit.;* Friedreich, *loc. cit.*

[10] Thurnam, *Medic. chir. Transact.*, vol. 21 (second series, vol. 3), London, 1858, p. 250.

[11] Ecker, *Ueber aneurysmat. Ausdehungen der Herzklappen. Heidelberg. Med. Annal.*, 8, 1842, p. 152.

[12] Rokitansky, *loc. cit.*, vol. 2, p. 290.

[13] On this subject see, in addition to the authors already cited: Hodgkin and Jackson in *Medico chirurg. Transact.*, London 1846, vol. 29; J. M. Charcot, *Comptes rendus et mémoires de la Société de biologie*, 1851, vol. 3 and series 2, 1855, vol. 2; E. Lancereaux, Paris thesis, 1862, p. 35.

[14] Virchow, *Archiv für Pathol. Anat.*, 1857, vol. 10, parts 1 and 2, p. 183.

[15] Virchow, O. Beckmann, *loc. cit.*

time that the destruction of the endocardium is taking place. In support of this new concept there are now two groups of observations. The first includes the cases, which are really the majority, in which ataxic and adynamic symptoms are dominant. Prostration is extreme, the temperature is very high. There are irregular chills, somnolence, subdelirium or intense delirium. The tongue is dry, the spleen may be very large. At times there are signs of bronchial catarrh as well as meteorism and diarrhea. Sometimes ecchymotic spots and sudamina appear on various parts of the body. The disease is continuous and imitates, often to a confusing degree, the picture of typhoid or even more precisely exanthematic typhus.[16] Cases of the second kind are more reminiscent of purulent infection: repeated violent chills are superimposed upon ataxic and adynamic symptoms.[17] More or less severe jaundice has occurred repeatedly in cases of both categories,[18] and it is hardly doubtful that certain symptoms which have been attributed to icterus gravis really belong to acute ulcerative endocarditis. Must we assume that all the symptoms which have been discussed are due to an intoxication caused by the presence in the blood of a special morbid poison produced continuously on the diseased endocardial surfaces at the expense of the products of regressive change which that organ undergoes? This hypothesis has been advanced by almost all the authors who have studied the subject. We shall merely mention it, recognizing that it has much in its favor. In this connection emphasis should be laid on the fact that the typhoidal state is merely a phenomenon of secondary importance. It always follows several days after the endocardial disease which alone can explain its development and to which it apparently attaches itself as a secondary disease.

The local symptoms are those of acute valvular endocarditis, with the difference that since the morbid process generally does its destructive work in a short space of time, careful and frequently repeated observation can often follow the advances virtually day by day. This is what happened in the case which forms the main object of the present note. In a case of the same kind which one of us studied at La Pitié two years ago in a woman in the eighth month of pregnancy, the most marked signs of aortic insufficiency developed progressively within nearly eight days.

To complete this brief sketch of typhoidal ulcerative endocarditis, we must add that this disease seems to occur especially in debilitated persons, especially in the puerperal state;[19] that it has been observed repeatedly during acute articular rheumatism supervening in cachectic persons;[20] and that sometimes it appears to have been present from the beginning, without having been preceded by any recognizable disease.

Inevitably, cases of this kind will become more common in any hospital the more the physician learns to recognize them. Our case shows that nowadays, at least in certain favorable circumstances, they can be diagnosed with a degree of accuracy.

This case differs in several respects from those which have been reported up to now. The ulceration was located in the right heart on the tricuspid valve. There were no infarcts in the spleen, kidneys, or other viscera. Their place was taken, so to speak, by numerous suppurative foci in the two lungs. Several other peculiarities were observed, which we shall describe in the case report.

Ulcerative disease of the tricuspid valve. Typhoidal state. Death thirteen days after onset. Multiple lung abscesses.

Alphonse V., age 27, plumber, entered the Hôtel Dieu, Sainte-Jeanne ward no. 5, on November 4, 1861. The patient was of vigorous constitution. He said he had never had sickness of any kind and had been in perfect health until October 30, 1861. On that day, after having fatigued himself excessively in taking care of his very sick wife, he was seized with a

[16] Virchow, S. Kirkes, Bamberger, Friedreich, *loc. cit.*

[17] *Id.*

[18] A short time after the presentation of the case under discussion Dr. Lancereaux submitted to the Society of Biology a case of that kind. Frerichs' case 10 (*Klinik der Leberkrankheiten*, vol. 1, 1858, p. 171) and perhaps Budd's case 9 (*On Diseases of the Liver*, second edition, London, 1852, p. 255) may be compared to the case of Dr. Lancereaux.

[19] Acute endocarditis appears quite frequently during pregnancy or the puerperium, when it at times assumes the ulcerative form. On this point see: Virchow, *Verhandl. der Gesell. für Geburtskunde*, vol. 2, 1858, p. 409 and *Gesamm. Abhandl.*, p. 711. Bamberger, Friedreich *loc. cit.* Simpson, *Obstetric Memoirs*, vol. 2, p. 67, 70. Lotz, *De l'état puerpéral considéré comme cause d'endocardite* (*Bulletin de l'Acad. de méd.* and *Union méd.*, May 14, 1857). Westphal, *Endocarditis ulcerosa in puerperium*, *Virchows Archiv*, vol. 20, parts 5 and 6, p. 542, 1861.

[20] A case presented by one of us at the Société de Biologie in 1851 is an excellent example of this kind, although it was not given at that time the interpretation that we give it today. See *Comptes Rendus de la Société de Biologie*, vol. 3, p. 80.

violent chill, headache, and intense lumbar pain. A physician prescribed a purge, then an emetic and ordered the application of a plaster over the region of the liver, which had begun to pain severely. Since these treatments brought no relief, the patient decided to enter the hospital.

He was examined carefully on morning rounds on November 5, but detailed note of his condition was not made. He showed all the characteristics of a typhoidal affection at its onset: he had fever, a depressed appearance, tongue covered with a yellowish coat, headache, and slight cough. No epistaxis. The abdomen was prominent and tender to pressure; there was no diarrhea. Over the heart there was a blowing murmur maximal at the base and during the first heart sound. This murmur was rather loud. The urine was treated with nitric acid and heat and proved to be highly albuminous. Two glasses of Sedlitz water were prescribed.

On November 6 the condition was about the same. The murmur was much fainter than before. The urine was not examined.

On November 7 the face was pale, the cheeks flushed, the eyes bleary, the pupils constricted. The intelligence was not much weakened. The memory was good but the patient had quite some difficulty in expressing himself. Although marked stupor was not present the general appearance of the face indicated the typhoid state. The skin was warm and covered with viscous sweat. The abdomen was ballooned out, tympanites was marked. There was a lenticular rose spot over the last false rib on the left side.

The tongue was dry and cracked; the mouth pasty; continual thirst; anorexia. Anything ingested was vomited. The pulse was full and frequent (128 per minute). There was a blowing murmur over the middle region of the heart, audible between the two normal sounds. Dyspnea. Fine subcrepitant rales at the bases of the lungs. Sibilant rales anteriorly. Percussion note approximately normal. Inability to urinate; the patient tried to void five or six times during the night but had no success. He was catheterized; there was no albumin in the urine.

November 8. The patient slept a little during the night and had no delirium. In the morning there was sweat over the entire skin. Markedly stuporous expression. Nostrils dry. Left pupil constricted; the right pupil showed old atresia dating from a disease which could not be identified from the patient's statements.

Vague headache; a little giddiness in the sitting position. The patient did not remember whether he had urinated or defecated; apparently he had passed some urine and had had a diarrheal stool. No pain in the extremities. The subcutaneous veins of the upper limbs appeared well developed.

Pulse frequent (128 per minute), strong, and somewhat bounding. No sensation of palpitation or suffocation. Cardiac impulse not exaggerated. Blowing murmur very distinct, a little rough, in the second part of the cardiac cycle, and fainter blowing murmur in the first part. The maximum of these murmurs was at the base. At the moment of inspiration there was a kind of modification of the heart sounds, a sort of vague rub. The respiration was faster than normal. Percussion and auscultation gave the same result as on the previous day. Tongue dry, rugae very prominent. Intense thirst. Abdomen a little less blown up. The lenticular macule observed on the previous day was absent. No colic. At night the patient again had mildly bilious vomiting. On re-examination the urine contained no albumin; no blue color with nitric acid. Two glasses of Sedlitz water; mustard applications.

November 9. Face more altered than yesterday: pallor. Nose slightly contracted; subicterus of conjunctivae. Pulse 128, strong, full, and bounding. Subcutaneous veins of upper limbs and neck engorged. Slept a little during the night; no agitation or delirium. No complaint of palpitation or dyspnea. Very distinct double blowing murmur, rough, brusquely emitted, toward the base of the heart, alternately weaker and stronger. At the base there is something like a brief rubbing or crumpling sound especially with some of the inspirations. Continuous blowing murmur over the vessels of the neck, with double murmur more or less obscured at times by the continuous murmur. Normal percussion note all over the chest. Fine subcrepitant rales posteriorly on both sides. Breath sounds sibilant here and there over the rest of chest. Infrequent cough. Tongue dry, markedly fissured, covered with a yellowish coat. Intense thirst. Vomited several times after the ingestion of liquids, *tisane*, or bouillon. The vomitus was greenish. No abdominal pain, no rose spots, constant marked tympanites. No stools despite Sedlitz water, which was not vomited. The spleen did not seem to be large; this had been the impression on the previous day, allowance being made for the difficulty of percussion during tympanites.

Since the patient had not urinated he was catheterized; the urine flowed out without receiving the least pressure from the bladder. Mustard applications; enemata with 30 grams of sodium sulphate. Bouillon.

November 10. The patient had been delirious during the night. He spoke loudly, sat up and shook his arms. Profuse sweat yesterday and last night. Vomited several times last night after taking bouillon. No urination. The purgative enema did not provoke defecation.

In the morning the facies was changed; pallor, with discontinuous redness of the cheeks; depression, appearance of stupor. The patient was calm and answered questions clearly. Sweat all over the skin. No pain in the chest or precordium. Venous pulse

very distinct in the external and internal jugulars. Veins of the superior and inferior extremities engorged. Pulse 128, very strong and bounding. Precordial dulness within normal limits. Cardiac impulse not exaggerated; no thrill recognizable. At about the middle of the heart there are two very distinct brief murmurs, the first not as rough as the second. The latter was rough, a true saw-murmur, abrupt. On auscultation at the level of the base of the heart or over the course of the aorta, only the murmur accompanying the first sound was audible and it was much less distinct there than over the middle of the heart; the murmur of the second sound was no longer heard and instead of this abnormal sound a distinct valvular sound was heard. Over the vessels of the neck on the right side a diastolic blow was heard very distinctly; the continuous murmur was no longer audible.

Percussion note normal but a little increased in the infraclavicular regions and in the center of the infraspinatus fossa. Breath sounds slightly sibilant at a few areas; subcrepitant rales at both bases, especially in the back.

Drink of julep containing 40 drops of tincture of digitalis; mustard applications; eight cups with scarification over the precordium; 45 grams of magnesium sulphate.

November 11. The patient had sweated profusely yesterday and last night. Although no purge was prescribed he had a dozen profuse liquid stools. Agitation and delirium yesterday evening until about midnight. At present he is calm but the agitation recurred about five o'clock this morning. In the daytime, shortly before ward rounds he was calm again. During the daily visit he was altogether quiet; he was a little somnolent but easily roused and replied clearly to questions. Face pale and indicative of stupor. Abundant mucous secretion in the conjuctivae, especially on the left.

The skin was hot and moistened with sweat. The subcutaneous veins of the superior and inferior extremities, the abdomen and neck were prominent. Pulse 124, weaker than yesterday. Precordial dulness scarcely passed the middle of the sternum and did not extend above the lower border of the third rib. At the level of the middle of the heart the double blowing sound was clearly audible, the second component being louder than the first, also rougher and quite brusque. At the base of the heart the murmurs tended to disappear and the normal second sound of the heart was clearly heard. At the neck there was a diastolic arterial blow. Venous pulse very distinct over the internal and external jugular veins.

Slight dyspnea; cough more frequent than on previous days. The patient complained of severe pain in the lumbar regions when he was made to sit. Subcrepitant and sonorous rales all over the chest posteriorly, without alteration of breath sounds and without dulness. From time to time at the moment of inspiration and at the level of the base, the beating of the heart, through pressure on the lung, produced a sound analogous to a dull subcrepitant rale.

Tongue very dry, and deeply fissured. Intense thirst. No vomiting. Abdomen greatly distended. No lenticular rose spots. No pain or tenderness in the abdomen. No pain or swelling in the joints. Urine obtained in large amounts by catheter was not cloudy. No albumin. No green or blue color with nitric acid. After a few moments the upper part of the urine showed a slight turbidity due to the liberation of a little uric acid.

The blood obtained by cupping was coagulated but the clots were large and soft, and little serum had separated.

Six cups with scarification applied over the heart; emollient enema, mustard applications, bouillon.

November 12. Yesterday the patient had several more liquid stools. He was delirious during the first half of the night. In the morning his face looked depressed. His head was tilted slightly backward. He was evidently quite weak. His replies were slow but clearly articulated. He said he felt very well. Pulse weak. Auscultatory findings same as on previous day. The blowing murmurs were slightly less distinct and were not clearly audible with each heartbeat. When the patient held his breath, after two or three heartbeats the murmurs became distinct again, especially that in the second part of the cardiac cycle. Moist rales all over the chest, without dulness. Lumbar pain again; abdomen distended. The subcutaneous veins were constantly prominent. No albumin in catheter specimens of urine; no contractions of the bladder; no blue color with nitric acid. Blood drawn by cupping had the same characteristics as yesterday.

Mustard plasters; emollient enema. Potion of diacodium with four grams of extract of cinchona.

Death occurred on November 12 at 7 P.M. and was not preceded by convulsions. Consciousness was preserved almost until the end.

Autopsy was made on November 14 at 10 A.M.

Cranial cavity. All parts of the brain were entirely normal. No injection of the meninges, no tuberculous granulations.

Abdominal cavity. Kidneys normal, not congested. The spleen was enlarged to about one and a half times the normal volume; the tissue was a little soft but not diffluent. The liver was voluminous, not much congested and without noticeable alteration. The gall bladder and common bile duct contained much bile. The intestines were blown up with a large amount of gas. The small bowel contained a large quantity of liquid matter, turbid, almost muddy, of greenish-gray color. Throughout the length of the small intestine, but especially in the ileum there were areas of redness produced by very fine arborizing injection of the mucosa; these reddened areas were rather close together and thus extended over a large part of the internal surface of

the intestine. The Peyer's patches and isolated follicles were entirely normal. The stomach was not examined.

Chest. The pericardium contained a small amount of fluid. There were no pseudomembranes on the parietal or visceral layer. On the anterior surface of the left ventricle, near the auriculoventricular groove, there is a whitish plaque of fibrous appearance, evidently old. When the apex of the heart was cut and water was injected into the aorta and the pulmonary artery, it was established that the aortic and pulmonic values were competent. The ventricles were then opened completely for examination of these valves and of the auriculoventricular valves. There were fresh fibrinous coagula in both ventricles.

Left side of the heart. Endocardium normal. Mitral valve normal although a little thickened at the attachment of the chordae. The aortic valves were of normal thickness. On two of the cusps the base was slightly detached at one of the points of origin on the arterial wall, but, as has been said, the valve was competent despite this. Slight thickening of the aortic wall within and near the origin of this vessel. This thickening was probably due to multiplication of the elements situated beneath the internal membrane. No atheromatous change.

Right side of the heart. The endocardium of the ventricle and auricle is normal. The anterior cusp of the tricuspid valve is normal in its external half but its internal half is thickened, opaque and perforated by an irregularly rounded opening half a centimeter in diameter on the margins of which there were small fibrinous vegetations. This perforation is situated 3 or 4 mm. from the free margin and the part of the valve between the perforation and the free margin is greatly softened. In addition to the small grayish granular fibrinous vegetations which have just been mentioned there was another vegetation, similar in appearance but larger, attached to the upper edge of the opening by a fibrinous pedicle. This was very mobile and, when lowered, could close the abnormal orifice completely. The vegetation was implanted on the ventricular surface of the valve fold. In other respects the ventricular surface of the fold was relatively little diseased when compared with the auricular surface. The latter was very uneven in its internal half, and mottled by small, easily detachable whitish gray eminences which seemed to be made mainly of deposits of fibrin and probably also by valvular tissue which was beginning to disintegrate. At the level of the adherent border of the valve and on the auricular side above the altered region, there were two little red spots consisting of injected vessels. There was no other injected area at any other point of the valve fold. The other folds of the tricuspid were virtually normal.

In the left ventricle, below the attachment of the innermost cusp of the aortic valve there was, on the interventricular wall, an opening which had dull margins formed by the endocardium, which was normal at that point and also over the rest of the ventricular cavity. This opening was almost as large as the tip of the little finger. It was shaped like a partly gaping buttonhole. It was the opening of a channel which ended, by another orifice, well defined but smaller, in the right ventricle. The latter orifice situated in the re-entrant angle between the altered antero-external cusp of the tricuspid valve and the internal cusp. Its diameter did not exceed 3 mm. The interventricular communication was evidently quite old and probably congenital.

The pedunculated yellowish-gray vegetation was tinted dark red over a large part of its surface and was implanted on the edge of the ulcerated opening in the tricuspid valve. Its structure was examined microscopically. The vegetation was made of fibrillary fibrin in the middle of which there were several erythrocytes but very few leukocytes. The diseased parts of the valve contained a deposit of fibrillary fibrin with very few oblong nuclei and still fewer fusiform cells. In the fibrinous substance there were many small fatty granulations and a few granular bodies. There were no nucleated pus globules and no pyoid globules. The blood contained in the right ventricle and that in a clot adherent to one of the little fibrinous vegetations on the ventricular surface were also examined; a very small number of leukocytes was found, certainly not more than are generally found in fresh clots,

Lungs. The lower parts of the lungs were adherent, especially posteriorly, and were hard to remove from the chest. Above the densely adherent parts, on the posterior surface of the lungs, there were thin pseudomembranous plaques which could be removed in large strips and which were of recent origin. The entire upper portions of the lungs were crepitant, the lower parts were only slightly so. There were places where the lungs were resistant to the pressure of the finger without being appreciably crepitant. The trunk of the pulmonary artery and the main branches on each side were opened and examined carefully; nothing abnormal. The mucous membrane of the bronchi was brightly injected.

In all the parts of both lungs there were many scattered abscesses of various size; the largest were not bigger than a small nut and these were very few. Most were as big as a hemp seed or even smaller. The smallest abscesses were spheroidal. The largest had an irregular shape and were lined by a fairly thick pseudomembrane. The liquid in these abscesses was yellowish gray; it contained many purulent and pyoid cells and many multinucleated cells. There were also several fibroplastic cells and cells of the pulmonary epithelium loaded with fatty granules. Both on the surfaces of the lungs and in the interior there were irregularly shaped ecchymoses which had some resemblance to small apoplectic foci. Not a single tubercle was found. In many places there were channels filled with a yellowish

white substance; these protruded from the cut surface. These channels ramified and seemed to belong to the pulmonary arterial system. The matter which filled and distended them was of cylindrical shape, branched when the channel was branched, and composed of a fairly thick yellowish white substance made of fibrin containing innumerable pus cells. These fibrinopurulent cylinders were surrounded by a very small amount of purulent liquid. Within the material which made up these cylinders it was not possible to discover fragments of fibrin which might have been detached from the fibrinous vegetations on the tricuspid valve.

In summary, this was the case of a young and vigorous man, who had always enjoyed good health. On several occasions the patient stated that he had never had trouble with his joints. Following overexertion during the illness of his wife, who had typhoid fever, he was seized with chills, stiffness in the joints, and severe headache. He was first observed five days after the onset of his illness. Prostration, headache and meteorism are the symptoms which appeared predominant; they seemed indicative of incipient typhoid fever. At the same time the surprising feature was the discovery of a cardiac murmur rougher than what is usually encountered in these circumstances.

In the next two or three days, in addition to the signs already mentioned, the patient showed stupor. The mucosa of the tongue became increasingly dry. In the skin of the abdomen there was a spot which was much like a lenticular rose spot, and bronchitis was present, yet the signs of a disease of the heart became increasingly clear. There was a double blowing murmur maximal at the level of the middle of the heart, and very marked during the second part of the cardiac cycle. There was severe constipation. The suspicion arose that this was not a case of typhoid fever. At last, on the fourth day after the patient's admission to the hospital, because of similar cases we suspected the typhoidal form of an ulcerative affection of the endocardium. During the last days of the illness the weakness increased and there were agitation and delirium at night, but the evidences of heart disease became increasingly definite and there was now no hesitation in supporting the diagnosis which had previously been made with great reservation. The patient died thirteen days after onset.

Autopsy showed that the Peyer's patches and the isolated follicles of the small intestine were perfectly normal. The only viscera which showed changes were the heart and the lungs. One of the leaflets of the tricuspid valve was thickened, uneven, and softened in its internal half. In the middle of this altered portion there was a perforation, evidently recent, on the margins of which there was detritus of a special type and also deposits of fibrin. One fibrinous vegetation, larger than the others and pedunculated, could have acted as a stopper for the abnormal opening. There was also a small congenital communication between the two ventricles. In the lungs, in addition to the lesions of bronchitis, there was a considerable number of small pneumonic foci, most of which contained abscesses which had been present for some time. There were also several interstitial ecchymoses which probably indicated the initial phase in the development of new abscesses and fibrinopurulent concretions situated in several fine branches of the pulmonary artery.

Thus the results of the autopsy confirmed the diagnosis.

The *diagnosis* was based principally on the development of cardiac symptoms in a man who had previously not had heart disease, on the distinct concomitant typhoidal state, severe constipation, and the rapid progressive aggravation of the illness without corresponding increase in the intensity of the adynamic and ataxic symptoms. The much greater frequency of changes in the left heart had first made us think that the disease was located on the mitral or aortic valves. At the same time in view of the fact that the louder murmur, that which occurred in the second part of the cycle, was not transmitted along the course of the aorta and that even at this level the normal second sound of the heart was audible and in view of the persistent distention of the subcutaneous veins of the limbs, trunk and neck, it was considered quite possible that the lesion might be situated on the valves of the right heart. This diagnosis was offered with great reservation. As has been shown, it was correct.

The *auscultatory signs* were very remarkable. We have just stated that there was a double blowing murmur, most intense in the second part of the cycle. These murmurs were loudest at the middle of the heart. The second component was not heard over the course of the aorta. Over the aorta and the arteries of the neck nothing was heard but a blowing murmur which coincided with the normal first sound but was much weaker than the sound heard over the heart during the same phase. This was undoubtedly an anemic murmur. In explaining the double cardiac murmur it is hard to know

whether to invoke in part the passage of blood from one ventricle to the other by way of the congenital interventricular channel. But it seems certain that the perforation of one of the tricuspid leaflets must have been the main cause of the abnormal sound. It must not be forgotten that this double murmur grew weaker or stronger from time to time and that occasionally it was almost imperceptible. This is explained easily enough if we think of the little fibrinous polyp which was implanted on the margin of the perforation and which from time to time must have occluded the anomalous opening more or less completely. During auscultation it was always thought that the first murmur coincided with the normal first sound and the second murmur with the second sound. It is possible that this was wrong, since the simplest way of explaining the double murmur is by assuming that the first component was caused by the passage of blood through the perforation during auricular systole (weaker murmur), while the second component was due to the passage of blood in the opposite direction through the same perforation during ventricular systole. Since the movements of the heart were frequent during the entire course of the illness, it will be readily understood how easy it was to be deceived as to the exact timing of each murmur.

The typhoidal state appeared three to four days after the onset of the disease. Probably for some time before the initial chill the morbid process was going on unobtrusively in the valve fold which was later to perforate. This first process was not accompanied by symptoms intense enough to attract the patient's attention. Doubtless the morbid phenomena became evident at the time when the first fragments of valvular debris were detached from the valve.

The pieces of softened valvular tissue and little fibrinous concretions which probably had already formed on diseased parts of the valve were carried by the blood current to the lungs. Perhaps the smallest of these particles would have been able to pass through the pulmonary circulation into the general circulation and mix with the arterial blood. These particles by their septic qualities could have caused the symptoms of intoxication. The less tenuous fragments were detained in small branches of the pulmonary artery, where they were found during the autopsy in the form of fibrinopurulent cylinders. Acting like irritating bodies, these capillary emboli were in all probability the origin of the little foci of suppurative pneumonia which were found in both lungs. This seems to us the most probable manner in which these abscesses were produced. Despite their incontestable analogy in many respects with so-called metastatic abscesses, we do not believe that they were the product of purulent infection in the strict meaning of the word. In support of this opinion we will point out that in our case the lungs were the only organs which contained abscesses, that at no point was there a trace of suppurative phlebitis, that the diseased parts of the tricuspid valve did not contain nucleated pus cells or pyoid cells, and that the general symptoms were not those usually encountered in true purulent infection, since the patient had only the single chill which marked the onset of the illness.

It is known from the interesting work of our colleague Dr. Leudet[21] that abscesses of the aortic wall, when they open into the lumen, can form the origin of a true purulent infection. Sometimes purulent foci form also in the thickness of the heart valves.[22] Probably in certain circumstances they can produce the same infection. Such facts of pathology must be distinguished from those which especially concern us here, although from the practical point of view they lead to almost the same consequences.

Finally, in order to anticipate possible criticism, we declare that we attach little importance to the term *ulcerative endocarditis*, which we have used so often in the present article. As long as the characteristics and limits of what we must understand by inflammation have not been definitively determined, it might perhaps be appropriate—and we willingly admit this—to use the less explicit designation of *acute ulcerative disease of the endocardium* for cases like ours, in which the valves show neither vascularization, nor pus, nor plasmatic cells.

* * *

Author's Comments

In order to place this remarkable case report in historical perspective it is necessary to consider the degree of advancement which medicine had attained by 1862.

Through the work of Virchow and his fol-

[21] Leudet, De l'aortite terminée par suppuration, de son influence sur la production de l'infection purulente. *Arch. gén. de méd.*, vol. 2, p. 575, 1861.

[22] Dr. Lancereaux has recently demonstrated to the Society a purulent focus which developed in the thickness of one of the mitral leaflets.

lowers the basic principles of thrombosis and embolism had been elaborated and much of the pathogenesis of "ulcerative" endocarditis had been untangled. The leadership in scientific research was now passing from France to Germany; this is quite apparent even from the footnotes of the present article, which refer mainly to German writers.

The principal gap in the understanding of ulcerative endocarditis was a knowledge of bacteria. Thus the typhoidal symptoms in the present case were attributed to "the presence in the blood of a special morbid poison produced continuously on the diseased endocardial surfaces."

Much had been learned about the valvular lesions, including vegetations, aneurysms and abscesses of cusps. It was even recognized that the pathologic process might be superimposed upon a previously damaged or previously intact valve and that disease of the left side of the heart was far more common than disease of the right side. It was known that the peripheral lesions were infarcts and not ordinary abscesses and that these lesions might occur not only in the spleen and kidneys but also in the brain, eye and skin. Fundamental to this entire body of special knowledge was the recognition of the endocardium as a separate structure.[23]

Concomitant with these important advances in the pathology of endocarditis were the advances in clinical understanding of the disease. At this time, before the discovery of bacteria and the creation of clinical bacteriology, the differentiation of individual febrile syndromes was a cause of much embarrassment to physicians. Cases of continued fever accompanied by stupor and delirium tended to be grouped under the generic designation of "typhus" or "typhoidal fevers." These terms, because of their practical convenience, persisted long after the differentiation of typhoid and typhus by William Gerhard of Philadelphia (1837) and others. In the genus of typhus-like fevers it was usual to discriminate *typhus abdominalis* (typhoid fever), *typhus exanthematicus* (typhus) and *typhus recurrens* (relapsing fever). In the case reported by Charcot and Vulpian the patient presented stupor varied at times by delirium, and it is one of the authors' objects to point out that this typhoidal state can occur in ulcerative endocarditis. In their excellent introductory paragraphs they remark that this disease may resemble typhus more closely than typhoid; probably they had in mind the hemorrhagic character of the skin lesions of typhus.

Another important element in the background of the Charcot-Vulpian paper is the advanced development of physical diagnosis and especially of auscultation of the heart. Indeed the diagnosis of ulcerative endocarditis in the present case was based on careful auscultation, frequently repeated.

Although auscultation and percussion were now well advanced, they had not yet destroyed the older art of inspection, nor had they in turn been enervated by roentgenology, electrocardiography and clinical chemistry. Consequently the present case report, despite its repetitiousness and occasional tautology, provides an instructive demonstration of conscientious medical examination.

In contrast with these great advances in pathology and physical diagnosis was the utter poverty of therapeutics. Charcot and Vulpian had nothing better to offer than mustard applications, purges and inadequate amounts of digitalis.

The diagnosis in the present case was based on (1) continued fever, (2) changing murmurs, (3) auscultatory signs in the lungs, (4) persistent engorgement of peripheral veins and (5) absence of peripheral embolism. Because of abdominal distention the spleen was never palpable. The diagnosis of ulcerative endocarditis of the tricuspid valve was made during life and confirmed at autopsy despite the complete absence of any laboratory tests except analysis of the urine. Postmortem examination revealed the presence of vegetations on the tricuspid valve, with softening and perforation. There was one surprise, viz. a patent subvalvular opening, probably congenital, in the interventricular septum. This part of the anatomical picture had not been detected during life. The authors considered the possibility that the orifice in the septum might have caused the murmurs; they concluded that the perforation in the tricuspid valve was chiefly responsible, since the murmurs were variable and this variation might be caused by intermittent passage of the pedunculated vegetation over the hole in the valve.

The paper by Charcot and Vulpian is an impressive example of what the conscientious physician can accomplish by simple clinical methods. In this fact lies part of its value for the modern reader.

[23] Jarcho, S. Descriptions of the endocardium by Bouillaud (1835) and Bichat (1800). *Am. J. Cardiol.*, 2: 767, 1958.

Case Reports

Congenital Aortic Stenosis in Siblings*

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FAMILIAL INCIDENCE of congenital heart disease has been reported in a limited number of cases. The most common occurrence is in siblings but it has been reported in other relatives, occasionally in more than two members of a family and in two or three generations on rare occasions.[1–15] Such cases were collected either incidentally during investigation of large series or by compilation of single reports. To date the number of reports published is about 175 to 200 pairs. Many of this total number may be dismissed for one of the following reasons: (1) the same observation may appear in different compilations, the total of which makes up the basis of the aforementioned estimation; (2) in cases occurring before 1945, without autopsy, the diagnosis was not always reliable; (3) in cases collected after this date the partner of the pair frequently was not subjected to hospital observation; the diagnosis was often incompletely defined ("morbus caeruleus," "congenital heart disease," "heart failure in infancy," etc.) and was based on very slender evidence such as dubious medical reports, death certificates, information obtained from relatives and other circumstantial evidence.

The bulk of the pertinent observations is made up of cases of tetralogy of Fallot and its components, e.g., pulmonary stenosis or atresia, dextroposition of the aorta and the ventricular septal defect. These are related through their common developmental pathogenesis; therefore, pairs are encountered with both subjects presenting not only the same malformation ("concordant" malformations) but also different types of the kindred congenital heart diseases ("discordant" malformations).[14]

This concept of concordance and discordance, so important in the study of twins, is a valuable principle in the study of familial congenital heart disease. For malformations other than those with common developmental pathogenesis, discordance in cases of familial incidence is exceptional, especially as the general incidence of these other malformations is less common. However, familial occurrence of congenital heart disease is far more frequent than could be anticipated from probability alone, clearly indicating an hereditary factor. The exact numerical expectation is controversial. Subsequent offspring of the same parents who have had a child with a malformation have a 20 per cent chance for the occurrence of some cardiac abnormality and a 2 per cent chance for the occurrence of the identical malformation, according to the calculations referred to by Taussig.[11] These earlier estimations, however, are based on insufficient data. According to more recent work[10] the incidence of congenital heart disease is 1.8 per cent in subsequent offspring of parents with one child born with cardiac malformation, six times the expectation of the general population (0.32 per cent). In keeping with this assessment, Campbell[14] has recently calculated the occurrence of congenital heart disease in siblings and other relatives as five times as frequent as the expectation for other people. Concordant malformations are strongly prevalent, in contradistinction to the earlier statements.[11]

Aortic stenosis is actually one of the least common types of congenital heart disease, representing only 3.8 per cent of cases in Abbott's[8] series of 1000, 3 per cent in Wood's[16] series of 900 and 3 per cent in the series of 460 reported by Campbell and Kauntze;[17] it is completely missing in other surveys.[10,18]

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TABLE I
Body Measurements

Case No.	Sex	Age (yr.)	Height (cm.)	Normal height range for age (cm.)	Weight (kg.)	Normal weight range for height and age (kg.)[21]
1 (Va. K.)	Male	4½	101	92–115	16.5	12–19
2 (Ve. K.)	Female	6½	113.5	94–135	19.4	15–24.5

In a series of 250 instances of aortic stenosis only 20 per cent of all cases were of congenital origin.[19] In all series reported, aortic stenosis is more prevalent in men; for instance, in Nadas' series[13] of sixty-seven cases there were five times as many men as women; and of seventeen cases reviewed by Kjellberg and associates[20] only two were girls. Thus, incidence of aortic stenosis in women approximates 0.5 per cent of all congenital malformations. However, the disease is probably not as uncommon[17] as hospital and autopsy statistics would suggest, since it may remain asymptomatic for many years and the congenital origin is difficult to ascertain in later life. Freedom from symptoms is peculiar to the congenital form of this valvular defect; in Wood's[19] series 85 per cent of the patients with aortic stenosis due to rheumatic fever had symptoms as compared to 28 per cent of those with the congenital form. Owing to these circumstances, reports on its familiar occurrence are rare. In a recent paper[14] reporting forty instances of familial congenital heart disease there are three pairs with aortic stenosis including one pair of sisters and a mother and son.*

In the present paper aortic stenosis in siblings of different sex is reported. This was associated with aortic incompetence in the female member of the pair.

Case Reports

The siblings are a boy, aged four and a half years (Va. K.) and his sister, aged six and a half years (Ve. K.), of Armenian descent. The parents and a younger sister, aged two and a half years, had no abnormal cardiac findings. The presence of a cardiac murmur had been noted two years previously in both patients at the age of two and one half and four and one half years, respectively. Neither sibling had a history of rheumatic fever, but the girl had had several attacks of sore throat which had necessitated tonsillectomy in July 1959. Both had normal sedimentation rates and serologic tests for syphilis were negative. Neither child had any physical complaints.

The two children did not present anomalies of body build; there were no signs related to Marfan's syndrome. Their mental status was in accordance with their age. Growth was within the normal range (Table I).

The blood groups were as follows: father, group O; mother, group A; Va. K. (Case 1), group O; Ve. K. (Case 2), group A.

CASE 1. The four and one half year old boy (Va. K.) had a brachial blood pressure of 100/80 mm. Hg. The thorax was not deformed. The apex thrust was felt within the fifth interspace inside the midclavicular line, slightly enlarged and markedly heaving. Over the major part of the upper anterior chest wall and precordium a harsh systolic murmur was heard with maximal intensity, grade 4, over the right second interspace parasternally; it was well transmitted to the right subclavicular area and much less to the left. It was also heard very faintly in the interscapular area. The first sound was merged with the murmur; the second was of normal intensity and was not split. The last third of systole and the whole diastole were pure. Abnormal auscultatory signs were increased with exercise and emotion. There were no visible or palpable vibrations of the carotid or other peripheral arteries. The radial pulse was small but less abnormal than anticipated in view of the cardiac findings.

Graphic Tracings: The auscultatory and palpatory phenomena are illustrated by the phonocardiograms and the carotid sphygmogram (Figs. 1 and 2). The *phonocardiograms* revealed a protosystolic decrescendo murmur with maximal intensity in midsystole ("diamond-shaped"); the last third of systole was silent; the second sound was well registered, its vibrations showing the highest amplitudes of the phonocardiogram. Diastole was silent.

The ballistocardiogram was of much reduced voltage, a peculiarity interpreted as an expression of the diminished ejection speed since the resting stroke vol-

* NOTE: After completion of the present paper a new instance of familial (valvular) aortic stenosis occurring in male siblings has been reported by Reynolds and associates,[39] verified by autopsy in one brother after sudden death at the age of four and a half years, by operation in the other brother at the age of nine years and four months.

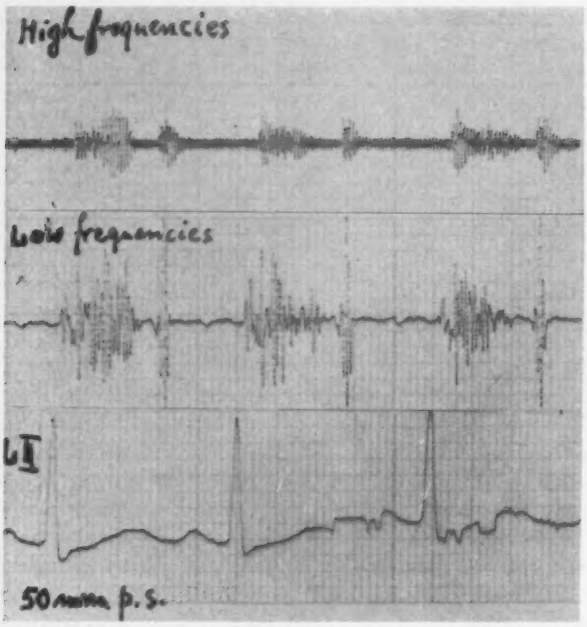


FIG. 1. Case 1. Phonocardiograms from aortic area. Procedure: microphone with air conduction bell; normal respiration. Paper speed is 50 mm. per second. Top row, high frequencies (150 c.p.s.); middle row, low frequencies (75 c.p.s.); bottom row, electrocardiogram, lead II.

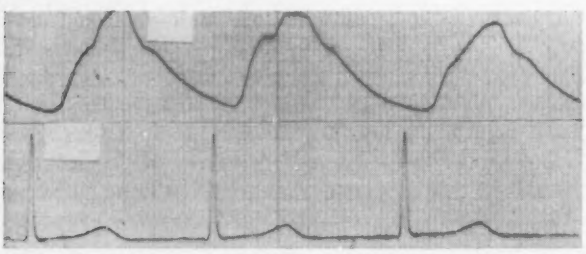


FIG. 2. Case 1. Carotid sphygmogram. Procedure: Schwarzer's photoelectric pulse recorder. Paper speed is 50 mm. per second. Top row, sphygmogram; bottom row, electrocardiogram, lead II.

FIG. 3. Case 1. Posteroanterior view of the heart showing the increased convexity of the left ventricular border and the prominence of the aortic knuckle.

ume remains within normal limits in subjects without heart failure.[19] The contour of the complexes was normal with moderate influence of respiration.

The carotid sphygmogram (Fig. 2) was typical of aortic stenosis: the gradient of the upstroke was so slow and the systolic peak so much delayed (0.20 to 0.24 second; normal values, 0.10 to 0.16 second) that an equilateral triangle resulted. The anacrotic shoulder changed position somewhat with the respiratory cycle but was not situated very low (0.09 to 0.13 second after onset; 40 to 60 per cent up the ascending limb), indicating a moderate degree of stenosis and/or its good compensation.[19,22] There was only a rudimentary catacrotic incisura with no after-vibrations. It was impossible to enforce arrest of respiration during registration; therefore, slight variations of pulse contour due to respiratory movements appeared in the tracing.

The radiologic examination (Fig. 3) revealed the

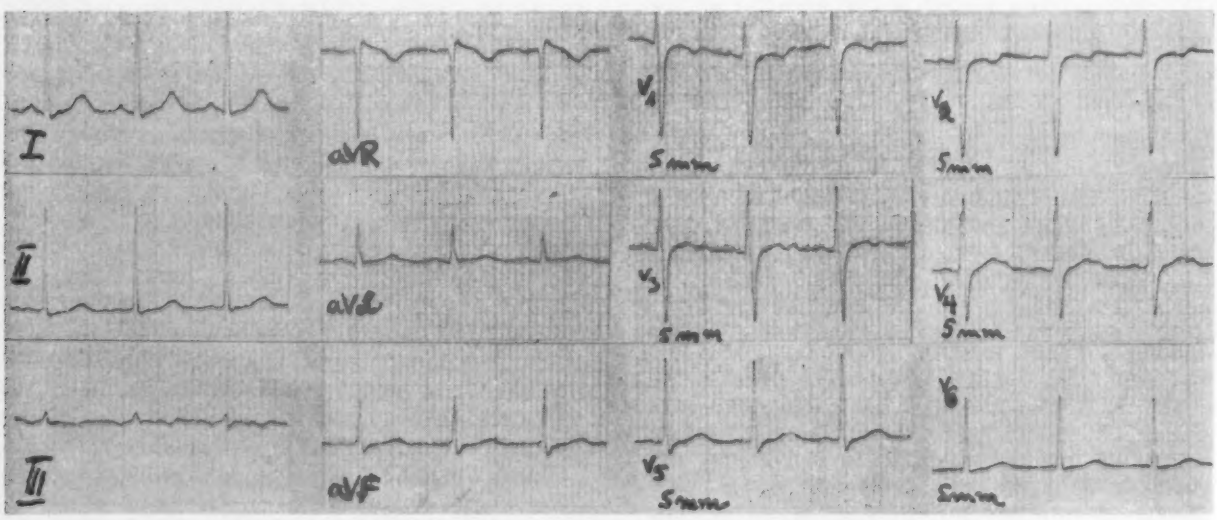


FIG. 4. Case 1. Electrocardiogram, precordial leads taken at half standardization.

following data: in the posteroanterior view the left ventricle was enlarged, as evidenced by the increased convexity of the left ventricular border; the aortic knuckle was prominent. In the left oblique view the unfolded aortic arch was noted. The left atrium, the chambers of the right side of the heart and lung vascularity were within normal limits.

The electrocardiogram (Fig. 4) showed a negative T in leads V_1 and V_2 and a diphasic T wave in lead V_3. These are normal features for this age group. Ventricular hypertrophy was suggested by the high voltage of the QRS complex that largely exceeded the normal values reported by Ziegler.[23] In view of the age of the subject, the absence of left axis deviation (QRS axis = +30°) in spite of left ventricular preponderance is a common feature.

CASE 2. The older sister (Ve. K.), aged six and a half years, had a brachial blood pressure of 90/55 mm. Hg. She presented a harsh, rasping systolic murmur, grade 6, best heard in the second and third interspaces to the right of the sternal border and transmitted to the whole precordium and part of the upper anterior chest wall, much more to the right than to the left. The first sound was merged with the systolic murmur; the second was perceived as an accentuation of this continuous murmur followed by a faint, blowing diastolic murmur best heard at Erb's point, persisting with diminishing intensity throughout the diastole. There was an intense thrill strictly confined to the second right interspace parasternally and not transmitted to the bordering areas. There were no visible or palpable vibrations of the carotid and radial arteries. The radial pulse was normal; by slight pressure on the finger nails, however, a capillary pulse was elicited. The apex beat was prominent, very forcible and markedly outside the midclavicular line.

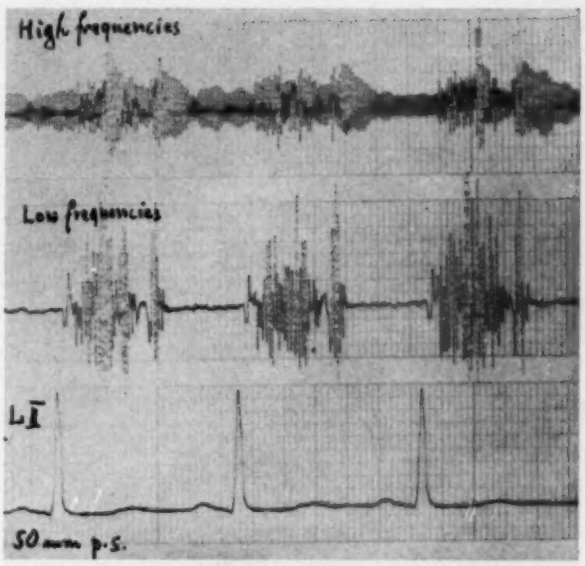
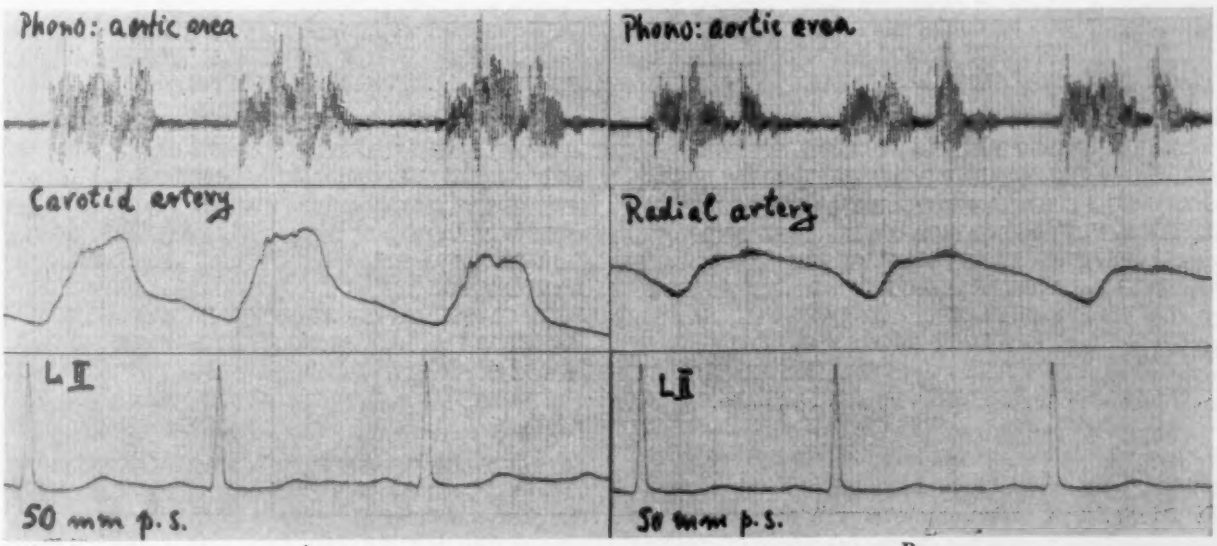


FIG. 5. Case 2. Phonocardiograms from aortic area. Procedure: microphone with air conduction bell; normal respiration. Paper speed is 50 mm. per second. Top row, high frequencies (150 c.p.s.); middle row, low frequencies (75 c.p.s.); bottom row, electrocardiogram, lead II.

Graphic Tracings: The *phonocardiogram* (Fig. 5) showed a holosystolic continuous murmur in the high frequency band; in the low frequency band, however, the low-pitched second sound was recorded after a silent interval. In fact, it was perceived as a sudden explosion-like accentuation of the systolic murmur. The very faint, high pitched, blowing, holodiastolic decrescendo murmur appeared only in the high frequency band and maximal amplification (with its well-known technical setbacks) was necessary to obtain a record (as is frequent for murmurs of this kind).



A B

FIG. 6. Case 2. Carotid and radial sphygmograms. Procedure: phonocardiograms, low frequencies (75 c.p.s.); sphygmogram as in Figure 2. Paper speed is 50 mm. per second. Top row, phonocardiogram from aortic area; middle row, sphygmogram; bottom row, electrocardiogram, lead II. A, carotid artery; B, radial artery.

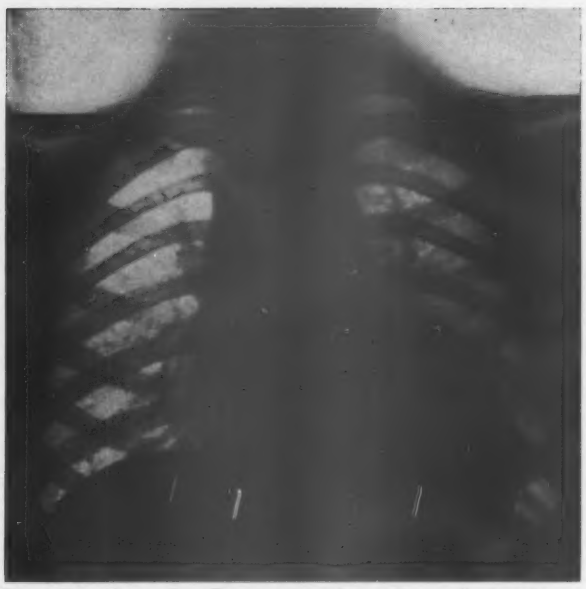


FIG. 7. Case 2. Posteroanterior view of the heart showing enlarged left ventricle with increased convexity of the ventricular border and markedly dilated ascending aorta and aortic arch.

FIG. 8. Case 2. Left oblique view of the heart revealing the marked jutting out of the ascending aorta.

The *carotid sphygmogram* (Fig. 6) was highly characteristic: its essential features were the slow upstroke (0.20 to 0.22 second; normal values: 0.103 to 0.16 second[19]) with approximately the same gradient as the downstroke and a large plateau with several indentations. There was a trivial anacrotic shoulder. The catacrotic incisura was rudimentary; the normal after-vibrations were missing. Contour and voltage were changing slightly because arrest of respiration could not be enforced during the recording.

Under the heading of "carotid shudder" the contour of pulse tracing previously mentioned has been described as typical of combined aortic stenosis and incompetence.[24] This actually would apply to the present case. The pulse contour could also be interpreted as a modified pulsus bisferiens in which the median trough is not shown (as is usual to some degree in direct aortic and brachial pulse pressure tracings), a concept in keeping with the diagnosis of combined aortic stenosis and incompetence. A similar tracing has been recorded in a corresponding case verified by operation.[19] Several other authors[25–28] however, have reproduced sphygmograms of the same contour with pure stenosis. Setting aside the conflicting views on this point, one may be satisfied that no such strongly abnormal tracing has been recorded in the absence of aortic stenosis.[6]

The radial sphygmogram (Fig. 6) was also characteristic for aortic stenosis. It showed a strongly convex, extremely slow upstroke (0.22 second). Furthermore, a phenomenon was noted which we have not found recorded in the pertinent literature in radial artery tracings (as opposed to carotid sphygmograms): during systole, from the onset of the first to the end of the second sound the pulse tracing showed a finely serrated edge like the blade of a saw which supposedly represented the transmitted vibrations of the thrill not recorded in the carotid tracing.

The *ballistocardiogram* in Case 2 was within normal limits, in contradistinction to the tracing of the brother (Case 1). This peculiarity was probably due to the coexisting valvular incompetence. The stroke volume, increased in aortic insufficiency, tends to counteract the effect on the ballistocardiogram of the reduced ejection speed brought about by the stenosis. In pure aortic incompetence such high voltages of the ballistocardiogram are observed that occasionally the body displacements produced by the cardiac impulses can be perceived with the naked eye.

The radiologic appearances of the heart (Figs. 7 and 8) denoted more advanced changes in the girl than were observed in her brother.

The left ventricle was enlarged with increased convexity of the cardiac border. Such changes were attributable mainly to hypertrophy. Furthermore, there was marked poststenotic dilatation of the ascending aorta and arch. The left atrium, the right cardiac chamber and the lung vascularity were unremarkable.

The electrocardiogram (Fig. 9) also denoted major changes. The high voltage of the QRS complex suggested hypertrophy and/or dilatation of the left side of the heart. In fact, the QRS voltages exceeded the normal values reported by Ziegler.[23] In spite of these alterations a normal electrical axis (+30°) was maintained. Furthermore, the ST-T complex was definitely altered in the standard leads (cup-shaped S-T segment, low voltage of T) and in leads V_5 and V_6 (S-T segment depressed, T nearly isoelectric). This too suggested left ventricular strain.

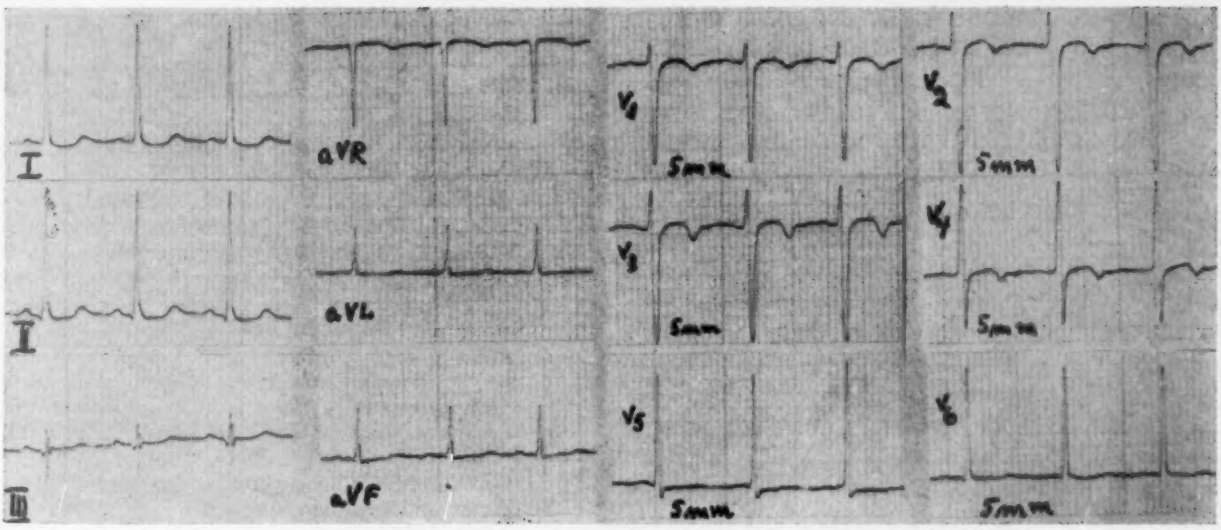


FIG. 9. Case 2. Electrocardiogram, precordial leads taken at half standardization.

A pertinent peculiarity to be stressed is the striking similarity of the electrocardiograms recorded in both siblings. The only difference was due to the presence of left heart strain in the girl. This finding demonstrates the fundamental identity of the cardiac structure in both subjects, including the most intricate details of the atrioventricular conduction system, the main cause of the infinite variability of electrocardiograms. Generally, such identity is encountered only in identical twins.

COMMENTS

In the two reported cases the diagnosis of aortic stenosis was made on the basis of the following findings: (1) presence of a systolic murmur of maximal intensity in the second right interspace parasternally with a thrill, both transmitted mainly to the right superior hemithorax; (2) radiologic and electrocardiographic evidence of left ventricular hypertrophy (and strain); (3) highly abnormal carotid and radial pulse tracings of the type noted in aortic stenosis or combined stenosis and incompetence; (4) presence of poststenotic dilatation of the ascending aorta and arch; and (5) absence of involvement of the left atrium, the chambers of the right side of the heart and the pulmonary circulation. These findings present the most convincing clinical evidence for the diagnosis. Of the classic signs, only valvular calcification and/or absence or weakness of the second sound were not revealed. Calcification of the valve, however, could not be expected in so early a stage of disease.

In a thorough study of the central pulse wave[29] some overlapping between slight abnormalities revealed in tracings of trivial aortic stenosis and "normal" pulse has been noted. This fact does not affect the significance of the highly pathologic tracings recorded in the present cases. It should be added that with careful recording there is practically no difference of contour in aortic stenosis (as opposed to incompetence) between (direct) arterial pressure pulses and (indirect) sphygmograms.[19] Moreover, the excellent sensitivity of the pulse recorder used in the present investigation is demonstrated by the rendering of minute vibrations in the radial sphygmogram (Fig. 6B).

In the absence of verification by operation or autopsy, direct evidence and evaluation of existing stenosis could have been obtained by the demonstration and measurement of a systolic pressure gradient between left ventricle and aorta.[22,30–33] Left heart and aortic catheterization, however, are only justified as a preparatory step to surgical repair in spite of the limited risk inherent in both methods.[19] Aortic catheterization is not considered for the present patients as long as they remain asymptomatic. The same considerations apply to aortic angiocardiography, by which in a few instances the differentiation between aortic and subaortic stenosis has been realized.[25,34,35]

In the girl (Case 2) the diagnosis of coexisting aortic incompetence was made on the basis of the following findings: (1) presence of a holodiastolic blowing decrescendo murmur with maximal intensity at Erb's point; (2) disproportion between the pulse pressure and the low systolic blood pressure and the demonstration of capillary pulse; (3) the recording of a carotid

pulse tracing considered by some authors[22,24] as typical for combined aortic stenosis and incompetence ("carotid shudder," modified pulsus bisferiens). However, for reasons mentioned previously limited value is attributed to this argument. The systolic murmur in the girl was peculiar because of its extension throughout systole, a feature much less common in aortic than in pulmonary stenosis[36] but not exceptional.[37] An explanation suggested by the present phonocardiograms is that the final part of the murmur does not show up at times in the customary low frequency recordings. The diastolic murmur, although otherwise typical because of the blowing high pitch and the decrescendo character, was also peculiar in view of its duration throughout diastole.

In both children the congenital origin of the stenosis was evident beyond reasonable doubt. In view of this common occurrence in pertinent cases of some degree of coexisting incompetence, the frequency of tonsillar infections in the girl's history is not a serious argument in favor of the thesis that the latter valvular defect was a complication due to superimposed subclinical rheumatic fever.

Although the existence of frank incompetency in one of the siblings suggests the valvular site of the malformation (in both), a definite differentiation between subaortic and valvular stenosis is not possible without the investigations referred to previously.

Summary

Familial occurrence of congenital aortic stenosis is reported in two siblings, a boy aged four and a half and his sister aged six and a half. The girl also had significant aortic incompetence.

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Patent Ductus Arteriosus in Identical Twins*

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THE presence of congenital anomalies in twins is of considerable medical interest and a variety of such cardiovascular anomalies have been reported.[1–14] An extensive review of the literature disclosed seven cases[2,3,11–13] of patent ductus arteriosus in supposedly identical twins; in six of the seven cases no evidence for monozygosity was presented. In none were any hemodynamic data recorded.

The cases herein reported are those of patent ductus arteriosus in monozygotic twins. Preoperative hemodynamic data, surgical confirmation and hematologic evidence of monozygosity were obtained.

CASE REPORTS

B. S. and E. S., twins A and B, are identical twin girls born to a twenty-seven year old gravida II para I mother after a full term pregnancy. One month prior to delivery the mother was admitted with a bloody show, but two attempts at induction failed. A single flat plate of the abdomen disclosed the twin pregnancy. Labor at term was normal and birth weights of the twins were 3,050 and 2,950 gm., respectively. No abnormalities were noted until the second year of life when precordial systolic murmurs were disclosed in both children. At age fourteen and a half months they both had chicken pox and later had measles, mumps and whooping cough, all without known sequelae. There was never any limitation of activity and both patients participated actively in sports. The patients, now twenty years of age, are employed as secretaries.

On physical examination the patients presented identical appearances in respect to carriage, body build and hair, skin and eye color (Fig. 1). General examination was also remarkably similar. The blood pressure was 134/56 mm. Hg., pulse 90, and respirations 12. Fundoscopic examination showed a slight arteriolar pulsation. The heart was not enlarged. The second pulmonic sound was slightly louder than the second aortic sound. Twin A had a classic machinery murmur maximal in the second left intercostal space 2 cm. from the sternum. Twin B had a grade 2 systolic murmur and a faint, early, low-pitched diastolic murmur, both maximal in the second left intercostal space. The remainder of the examination was normal.

Complete blood counts, urinalyses and blood urea nitrogen levels were normal. Twelve lead electrocardiograms and vectorcardiograms were within normal limits. Fluoroscopy showed the heart to be normal in size and configuration in both patients, although it was larger in twin B. The pulmonary artery was prominent and hilar pulsation could be seen.

The hemodynamic data are summarized in Table I. Indicator dilution curves were consistent with a small left to right shunt, being more evident in twin A than in twin B (Fig. 2). During the catheterization twin B was given 6 mg. of methoxamine intravenously with a resulting increase of 34 mm. Hg in the systemic-pulmonary arterial systolic gradient (Table I). During concomitant auscultation a typical machinery murmur was audible.

Both patients underwent *thoracotomy* and in each a small functioning ductus was found and ligated. No other cardiac anomalies were evident. Three months postoperatively a grade 1 systolic murmur could be heard over the pulmonic area in each patient. At fluoroscopy the hilar pulsation could no longer be seen.

COMMENTS

The preoperative diagnosis of patent ductus arteriosus was well established in the case of twin A although there was some doubt in the diagnosis of the case of twin B. However, in the latter case, intravenous administration of methoxamine, by elevating the systemic arterial pressure, brought out the typical machinery murmur. The use of a pressor substance to accentuate a cardiac murmur due to left to right intracardiac shunt has been reported by other workers.[15,16]

In addition to the identical appearance

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FIG. 1. Picture of the identical twins. E. S. (twin B) is on the left and B. S. (twin A) on the right.

TABLE I
Hemodynamic Data

Data	B. S. (Twin A)	E. S. (Twin B)
Oxygen content (vol. %)		
Right atrium	10.72	10.69
Right ventricle	10.53	10.22
Main pulmonary artery	11.49	10.96
Right pulmonary artery	12.02	11.10
Femoral artery	14.18	14.47
Blood flow (L./min.)		
Pulmonary	8.4	11.8
Systemic	5.5	8.3
Shunt (left to right)	2.9	3.5
Pressures (mm. Hg)		
Pulmonary artery	18/8	24/9; 32/11*
Femoral artery	136/65	135/68; 177/83*

* After methoxamine intravenously.

presented by the patients, blood grouping studies showed the patients to be identical with respect to OMNRh Kell and Duffy factors. Utilizing the method of Smith and Penrose[17] the probability of monozygosity on the basis of blood groups alone is 0.9160.

A great deal of information is available in the literature relative to the cause of patent ductus. Anderson,[14] Starer[11] and Lamy[18] agree on the increased familial incidence, and there is general agreement that rubella[14,19,20] in the first trimester may lead to patent ductus arteriosus, either isolated or complicated by other congenital anomalies. In separate retrospective studies, Anderson[14] found no increased number of pregnancy complications while Record and McKeown[21] found a significant increase of such complications. In five cases of patent ductus arteriosus from a prospective study of 5,964 pregnancies,[22] no complications of pregnancy were noted.

Other workers have noted birth order[21] and seasonal[14,19,20] factors.

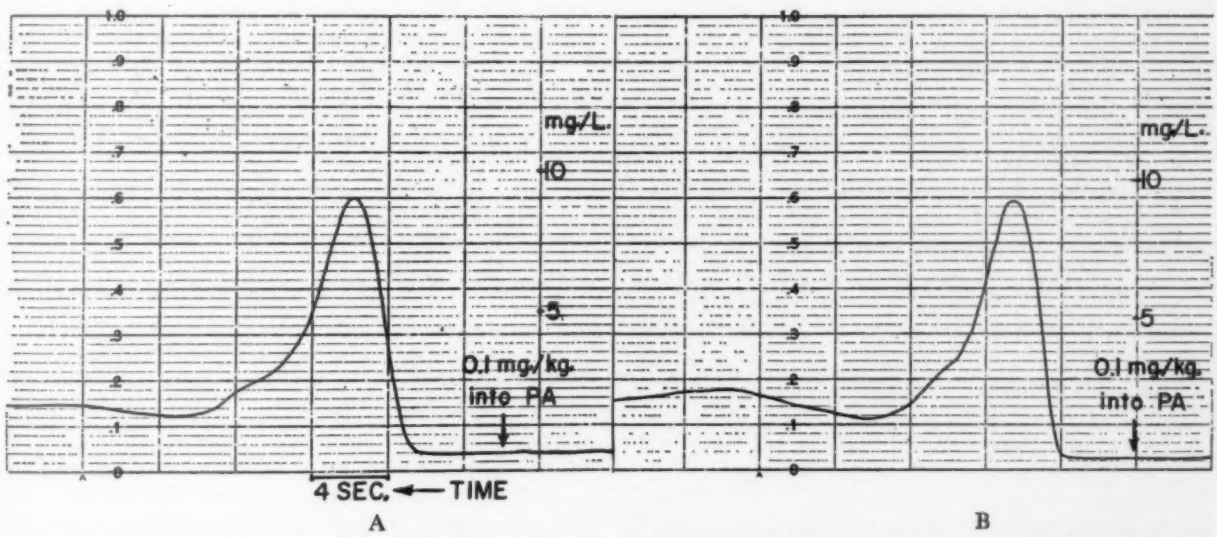

FIG. 2. September 30, 1959. Indicator dilution curves recorded in patient B. S. (twin A) from systemic arterial blood following injection of indicator into the pulmonary artery (PA curves). Curve A was inscribed at rest and curve B during exercise. Note the distortion of the terminal portion of the downslope, due to recirculation as a result of a small left to right shunt between the aorta and pulmonary artery. Tricarbocyanine dye II (cardiogreen) was used as the indicator. Curves are read from right to left.

Studies of twins in the literature show five discordant (only one twin affected) cases[1,8,11,14] in addition to the seven concordant cases mentioned previously. In four of the five discordant cases evidence of monozygosity is presented.

The results from the studies of twins also suggest that an environmental factor may play an important role. The fact that two of three ductuses are patent in patients two weeks of age[23] makes it problematic whether such an environmental factor is intrauterine or extrauterine.[8] It is likely that multiple etiologic factors, environmental and probably genetic as well, predispose to the persistent patency of the ductus arteriosus.

Summary

Cases are reported in which identical twins each had a patent ductus arteriosus confirmed by surgery. Hemodynamic data and evidence of monozygosity are presented.

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Ventricular Septal Defect with Aortic Insufficiency, Acute Rheumatic Carditis and Asian Influenza*

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VENTRICULAR septal defect associated with aortic insufficiency is uncommon.[1] Recently, however, a number of papers reporting such cases have appeared.[2–4] The case here described is of a patient who had this congenital anomaly complicated by acute rheumatic endomyocarditis. An attack of Asian influenza caused his death.

CASE HISTORY

D. E. was an eleven year old boy. A cardiac murmur was discovered in the first days of his life. He was not cyanotic even while crying. His physical development was retarded in infancy but improved later. Although the child was thin and poorly developed, he participated in school gymnastics without apparent discomfort.

In January 1957 a sudden change occurred. He had fever for three days and complained of marked tenderness at the right hypochondrium. He had dyspnea, palpitation and fatigue, and his physical capacity gradually diminished. During July 1957 a fever of 38°C. recurred and lasted for two to three days. Some days later the parents noted swelling around the eyes. Edema of the face increased and ankle edema was also noted. Urinalysis revealed albuminuria and hematuria, and the diagnosis of acute glomerulonephritis was then made in addition to congenital heart disease. In August, 1957 the patient was admitted to our department for the evaluation of his heart condition.

On physical examination, a chronically ill, emaciated, pale child was seen. His height was 144 cm. and weight 25 kg. Temperature was 37.5°C. but subsided to normal on the following day. Turicephalus was a prominent feature. The skin and mucosae were very pale and eye grounds were normal. The neck veins were moderately distended; slight venous and marked arterial pulsations were seen. The chest was symmetrical; the apex beat was visible and palpable in the sixth intercostal space in the anterior axillary line and was diffuse and heaving. Right ventricular uplift was palpable. A rough systolic thrill was felt over the whole precordium with the maximum intensity over the pulmonic area. Heart sounds were regular and clearly audible. The second pulmonic sound was accentuated and split. A harsh, grade 4 systolic murmur was heard with maximal intensity over the second and third left interspaces near the sternal border. This murmur was transmitted also to the neck arteries and was well heard at the back. A long, high-pitched diastolic murmur was audible in the same places so that an almost continuous murmur was heard. The pulse was collapsing and the peripheral arterial pulsations could easily be seen. Capillary pulsation was demonstrable. Blood pressure was 110/40 mm. Hg. The lungs were clear. The liver was palpated 4 cm. below the costal margin and was hard and slightly tender. The spleen was felt 2 cm. below the costal edge. There was no ascites and no ankle edema.

Laboratory Findings: Sedimentation rate was 57/93; red cell count was 3,750,000 with 10.6 gm. hemoglobin. Leucocyte count was 9,050 with normal differential count. Urinalysis revealed small amounts of albumin and a few leucocytes. Throat culture was negative for pathogens. The antistreptolysin O titer was 330 units/ml. and the C-reactive protein 5+. The electrocardiogram revealed combined right and left ventricular strain.

A roentgenogram of the chest disclosed marked enlargement of the heart in all directions (Fig. 1). The esophagus deviated sharply for a length of 1.5 cm. to the left and anteriorly on top of a right aortic arch. The pulmonary artery segment was prominent. The branches of the pulmonary artery were overfilled, especially at the left hilum.

The patient was treated with digitalis and diuretics. On the seventh day of hospitalization the temperature began to rise and reached 39°C. Since such spikes were noted also in the past, subacute bacterial endo-

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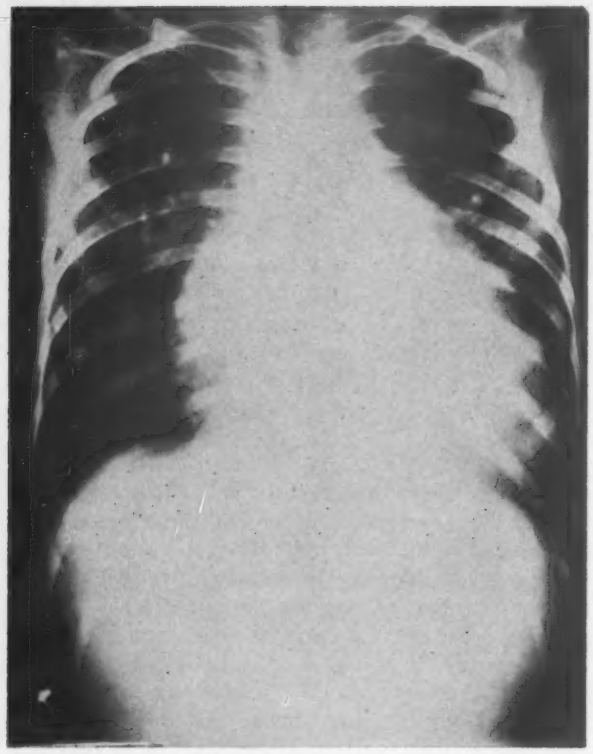

FIG. 1. Chest film showing generalized cardiac enlargement.

FIG. 2. Gross specimen of heart showing membranous ventricular septal defect.

carditis was suspected. Although repeated blood cultures were negative, the patient received 3 million units of penicillin and 1 gm. of streptomycin daily. The temperature returned to normal in four days.

Differential Diagnosis: The sudden congestive heart failure, together with the physical findings, made perforation of a sinus of Valsalva aneurysm the presumptive diagnosis. Subacute bacterial endocarditis, which was suspected, is known to accompany this lesion. However, the differential diagnosis included other possibilities, such as patent ductus arteriosus, aortopulmonary window or ventricular septal defect with aortic insufficiency. Further studies were therefore undertaken.

TABLE I
Cardiac Catheterization Findings

	Oxygen Saturation %	Pressure (mm. Hg)
Vena cava, superior	36	...
Vena cava, inferior	26	...
Right atrium, high	49	20/13/16
Right atrium, low	54	...
Right ventricle	76	63/15/36
Right pulmonary artery	75	65/25/47
Left pulmonary artery	72	...
Right brachial artery	97	105/40/70
Right femoral artery	97	...

Right heart catheterization was performed (Table I). The results demonstrate the presence of a double gradient of oxygen saturation, first between venae cavae and right atrium, second between right atrium and ventricle.

Retrograde Aortography: A polyethylene catheter was introduced through a Seldinger needle into the femoral artery and advanced up to the aortic valves. X-ray films were taken in posteroanterior and left-lateral views. The aorta was well visualized. No radiopaque material was seen in the right atrium, right ventricle or pulmonary artery; however, the pictures were not satisfactory technically and were interpreted as being equivocal. Therefore, a second catheterization was done. The results were practically identical with those obtained in the previous examination.

Terminal Course: The most probable diagnosis then was ventricular septal defect with aortic insufficiency, congestive heart failure and subacute bacterial endocarditis. The renal involvement found two months previous to admission could be explained by the subacute bacterial endocarditis. After continuous treatment with antibiotics and cardiac drugs, the general condition of the child improved. The sedimentation rate decreased, the antistreptolysin O

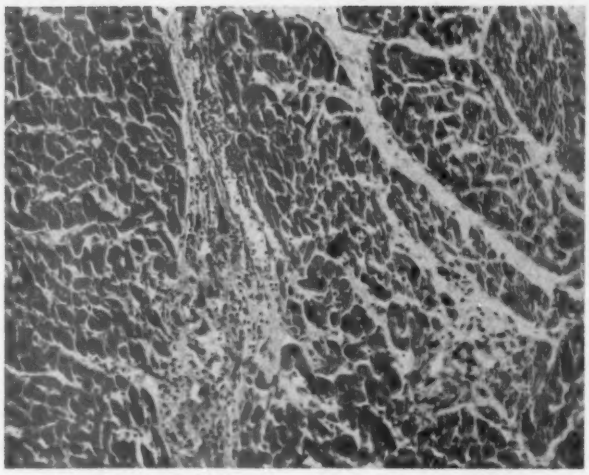

FIG. 3. Microscopic section of heart showing numerous Aschoff bodies.

titer became normal, 166 units/ml., and the C-reactive protein was negative. Leucocyte count was 7,500.

Arrangements were made to send the child for open heart operation. At this time an epidemic of Asian influenza broke out in Jerusalem, which apparently developed in this child. After two days of moderate fever, extreme dyspnea developed suddenly and the patient died in pulmonary edema.

Autopsy Findings: The heart was enlarged, weighing 490 gm. The thickness of the left ventricular wall was 16 mm. and of the right ventricular wall, 10 mm. The pulmonary conus was hypertrophied and measured 6 mm. The aorta arose from the left ventricle alone and formed a right aortic arch. The pulmonary artery was of normal position and was widened. The ductus arteriosus was completely occluded. The atrial septum was intact. In the membranous portion of the ventricular septum a round defect (15 mm. in diameter) was found, the edge of which was covered with fibrous tissue (Fig. 2). Similarly, fibrous thickening of the endocardium was seen in the pulmonary conus opposite the site of the septal defect. The aortic valve ring, which was just above the defect, was dilated (60 mm.). The aortic valve leaflets were thickened and incompetent. The sinuses of Valsalva appeared normal. The tricuspid ring was dilated.

On microscopic examination of the heart the classical picture of acute rheumatic endomyocarditis was found, with many Aschoff bodies (Fig. 3).

The lungs exhibited acute bronchitis, bronchiolitis, bronchopneumonic foci and hemorrhagic edema. In the liver focal necrosis was found. The spleen was septic and markedly congested. The virus of Asian influenza (A/Singapore/1957) was cultured from the lungs. Bacteria were not found.

COMMENT

A number of authors have emphasized that it is difficult to diagnose ventricular septal defect associated with aortic insufficiency[1,5–7] since other malformations can produce similar signs and symptoms. Scott et al.[2] in their recent article reviewed the literature and described correctly diagnosed as well as misdiagnosed cases. From their paper as well as from the works of others, it is evident that the malformation under discussion has often been erroneously thought to be patent ductus arteriosus, aortopulmonary window, ruptured sinus of Valsalva aneurysm and a long series of congenital and acquired anomalies.

In the case under review, the sudden appearance of congestive heart failure, the clinical picture of subacute bacterial endocarditis, the thrill and the to-and-fro murmur in the second to fourth left interspaces and the wide pulse pressure led to the presumptive clinical diagnosis of a ruptured aneurysm of the sinus of Valsalva. The "double gradient" at right heart catheterization, pulmonary hypertension and normal arterial oxygen saturation were compatible with this diagnosis. A retrograde aortogram was therefore performed which, for technical reasons, was not decisive. However, it was possible to establish that no filling of the right atrium, ventricle or pulmonary artery followed the injection of the contrast medium into the ascending aorta. Taking these findings into consideration, the diagnosis of ventricular septal defect with aortic insufficiency seemed to be the most likely.

The postmortem examination confirmed the presence of the suspected lesions. The fibrous thickening in the right ventricular outflow tract, observed in our case, was interpreted as a mechanically produced lesion by the impact of the blood coming through the septal defect from the high pressure area of the left ventricle.[8]

The histologic findings in the heart, the characteristic signs of acute rheumatic endocarditis and myocarditis with a large number of Aschoff bodies, were a considerable surprise to us despite the previous findings of elevated sedimentation rate and antistreptolysin O titer and positive C-reactive protein.

Finally, Asian influenza developed which was at its peak incidence at that time. Although this virus caused severe complications, including death, even in patients with no antecedent diseases, fatal consequences appeared more frequently in patients with previous heart disease. The virus, which was isolated from the lungs and identified as the Asian type, led to very rapid development of bronchopneu-

monia, bronchiolitis and hemorrhagic pulmonary edema. It is claimed that the pulmonary edema is due to the toxic effects of the virus; nevertheless, the abnormal hemodynamic conditions in the pulmonary circulation of this patient were certainly an additional factor in the development of the fatal complication.

Summary

A patient with the infrequent combination of ventricular septal defect with aortic insufficiency, complicated by acute rheumatic endomyocarditis is described. This patient died from pulmonary edema precipitated by Asian influenza.

Acknowledgment

We are indebted to Dr. A. Laufer of the Department of Surgical Pathology, for the histopathologic findings.

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Acquired Interventricular Septal Defects Due to Myocardial Infarction and Nonpenetrating Trauma to the Chest*

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WITH INCREASING proficiency in open heart surgery attention should be focussed on acquired interventricular septal defects. These are of two types: those occurring after a coronary occlusion with myocardial infarction and, less frequently, after nonpenetrating trauma to the chest wall. The pathologic clinical and hemodynamic findings in acquired interventricular septal defects of both types are described in this report.

ETIOLOGY AND PATHOLOGY

POSTINFARCT SEPTAL RUPTURE

Incidence: Perforation of the interventricular septum complicating myocardial infarction occurs as a sequel to coronary occlusion. Involvement of the septum can be demonstrated in 70 per cent of all types of infarcts. The left coronary artery, which perfuses the anterior two-thirds of the septum, is involved in myocardial infarction three times as often as the right. Wartman and Hellerstein[1] studied 235 infarctions occurring in 160 patients. The anterior half of the interventricular septum was involved in 54 per cent of the anterior infarcts of the left ventricle; the posterior half of the interventricular septum was involved in 25 per cent of posterior infarcts.

Eighty-two cases of perforation of the interventricular septum have been reported by Swithinbank.[2] The site of perforation was in the lower part of the septum in fifty-four of eighty-two cases (66 per cent), in the posterior part in fourteen cases (17 per cent), in the middle part in eleven cases (13 per cent) and is the superior part in only three of eighty-two cases (4 per cent). The size of the perforation varied from a pinhole to several centimeters; these larger measurements apply to linear tears. In five cases multiple perforations were present. Of the forty-six cases reported in detail the greatest measurement of the perforation exceeded 20 mm. in seven, was 10 to 19 mm. in twenty-three, 5 to 9 mm. in six and less than 5 mm. in ten.

Etiology: Numerous etiologic factors have been considered important in production of perforations after myocardial infarction[3]: (1) hypertension, (2) previous myocardial infarction, (3) heart failure, (4) anticoagulant therapy and (5) physical activity. Edmonson and Hoxie[4] reported thirteen cases (16 per cent) of interventricular perforation in seventy-nine cases of myocardial infarction ruptures. Their clinical data seem to support the conclusion that a blood pressure of 140/90 mm. Hg or above resulted in an increased incidence of myocardial rupture. The proportion of rupture was higher in those patients with small hearts, i.e., no preceding cardiac failure, and was lowest in those patients with large hearts and a low blood pressure. Cardiac rupture is most likely to occur after the first infarct, and is extremely rare in persons under fifty years of age.

Previous myocardial infarction with resulting fibrosis and development of collateral circulation of the interventricular septum results in a decreased incidence of septal perforation.[5] Chronic decrease of coronary flow and the resultant increase in fibrosis may be a factor in protecting against septal perforation. Lack of ischemia acting as a stimulus for the promotion of collateral blood supply results in more extensive myocardial necrosis in the septum.

Pathologic evidence has accumulated that

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institution of *anticoagulant therapy* in patients with an acute myocardial infarction has increased the incidence of myocardial rupture,[6] but Maher et al.[3] could not demonstrate a significant increase in their study. The problem as to why anticoagulation should increase myocardial rupture has not been elucidated and further study will be necessary to evaluate the importance of anticoagulation as an etiologic factor.

No real significance can be attributed to a possible increase in incidence of cardiac rupture in patients who are treated with the arm-chair method following myocardial infarction.[3] However, in cases studied in which there was extreme exertion by the patient, Maher and others[3,5] have believed that cardiac rupture was more common.

Cases of postmyocardial infarction rupture have been studied for other etiologic factors, such as shock, and therapy with vasopressor drugs, diuretics and antibiotics. The importance of these factors as a cause of septal perforation has not been elucidated.[7] It has been speculated that the perforations occur as tears in the weakened fixed septum as a result of the relationship between the muscle bundles to each other during their action.[5] Tears in the septum are the common finding whereas "blow-out" perforation is rare.[3]

RUPTURE AFTER TRAUMA TO CHEST

Nonpenetrating trauma to the chest has resulted in myocardial contusions, hemopericardium and rupture of the interventricular septum.[8] Rupture of the septum occurs rarely as a complication of chest trauma, and approximately twenty-five cases have been reported in the English literature. Experimental studies with dogs have shown that rupture is most likely to occur if the heart is struck in late diastole or in early systole.[9] The majority of patients have incurred their chest injuries during automobile accidents and the factor of extreme changes of intrathoracic pressures during deceleration has aroused some speculation.[10] Autopsy studies usually demonstrate jagged linear lacerations occurring near the apex of the heart below the membranous portion of the interventricular septum.[11]

Clinical Findings and Diagnosis

POSTMYOCARDIAL INFARCTION

Although reference is made to approximately 200 cases of acquired interventricular septal defect due to myocardial infarction,[12] about 113 cases can be found in the available English literature.[2] When first described only a few were diagnosed antemortem, but recent awareness of the problem has resulted in an average of about 70 per cent of cases being diagnosed correctly prior to death.

Clinical Features: The age group and sex distribution of patients with this lesion correspond to that of myocardial infarction in general. After myocardial infarction, cardiac rupture occurs most frequently on the third to twelfth day, the average being 7.4 days.[4] Interventricular septal perforation will present with the sudden appearance of a harsh systolic murmur over the precordium (97 per cent of cases),[2] best heard at the fourth and fifth intercostal spaces to left of the sternum. This murmur is accompanied by a systolic thrill (66 per cent of cases[2]) best felt in the same area. The acute onset of murmur and thrill is heralded by a recurrence of anterior and substernal chest pain and a sudden drop in blood pressure. Acute left heart failure and pulmonary edema also can signify the onset of the septal rupture. The electrocardiogram, which previously had shown evidence of an acute myocardial infarction with or without conduction abnormalities, will usually demonstrate a shift in QRS axis toward the right and the concomitant presence of a conduction defect, e.g., bundle branch block or A-V block.

Differential Diagnosis: The simultaneous appearance of these findings establishes the diagnosis, but one must consider the other probabilities:

1. *Ruptured chordae tendineae:* In this condition the systolic murmur is more localized to the apex and a systolic thrill is usually absent. Further chest pain and fall in blood pressure may or may not occur, but shift in the electrical axis of the electrocardiogram to the right will not occur and, on the contrary, may become more leftward as a result of the valvular insufficiency which may appear.[12]

2. *Ruptured papillary muscle:* The harbinger of this complication is acute pulmonary edema as well as an apical systolic murmur. The severe degree of mitral insufficiency results in fulminating, rapidly fatal acute pulmonary edema. A diastolic murmur may be heard at the apex.[13]

3. *Functional mitral insufficiency:* This condition may result in a pansystolic apical murmur due to dilatation of the mitral ring as a

result of left ventricular dilatation. However, this occurs gradually rather than suddenly.[14]

4. *Tricuspid insufficiency:* A systolic murmur of tricuspid insufficiency, functional or organic, is best heard at the fourth and fifth left parasternal region, and can be associated with a thrill in some cases. Respiratory maneuvers can be helpful in differentiation since a tricuspid murmur would tend to increase on inspiration whereas the ventricular septal defect murmur would tend to decrease.

5. *Acute pulmonary embolus:* Significant pulmonary embolism from the right heart or peripheral venous thrombosis may result in a clinical picture of chest pain, drop in blood pressure and shift in QRS axis but the precordial systolic murmur and thrill are absent.

Of course, the definite diagnosis of a septal perforation can be made by right heart catheterization, which will be discussed later. Nevertheless, the antemortem diagnosis can be made if one is aware of the entity.

Prognosis: The prognosis of postmyocardial infarct septal perforation is grave. Over 50 per cent of patients die within the first week[14] and only about 13 per cent will survive up to two months. A rare patient may survive as long as four to five years.[3] In those cases in which survival has lasted up to two weeks, there is usually a phase of right heart failure. This is in part due to the increased strain in the right ventricle and the left to right ventricular shunt.

POST-NONPENETRATING TRAUMA

Acquired interventricular septal defect secondary to nonpenetrating trauma to the chest is a rare occurrence, but with the increasing number of steering wheel chest contusions, we should be aware of its existence. In a review of 168 cases of nonpenetrating chest wounds at autopsy, eleven had tears in the interventricular septum.[11] Most cases occur in younger patients and in males. There are about twenty-three cases reported to date in the literature, eight of which have been proved by catheterization. No particular chest wounds are found superficially in these cases.

The development of a systolic murmur and thrill, maximum in the fourth and fifth left intercostal spaces adjacent to the sternum, signals the presence of the tear in the septum. No murmurs or thrills may be elicited initially perhaps as a result of hypotension. The electrocardiogram usually will show right axis deviation and sometimes a right ventricular hypertrophy pattern. A diastolic murmur often is heard over the second and third left intercostal space most likely as a result of a functional pulmonary valve insufficiency. If the rent is over 2 cm. in length a diastolic murmur may be heard due to the septal rupture.[15]

The differential diagnosis includes not only the previously discussed conditions but also the presence of a pre-existing congenital defect. Since we are dealing here with a younger age group this is a possibility. The factors which aid in the establishment of an acute acquired lesion are: (1) records or history demonstrating the absence of a previous interventricular septal defect; (2) progressive changes in the electrocardiogram from a normal axis to right axis deviation; and (3) the occurrence of an abnormal rhythm or conduction defect not previously present.

The prognosis of this acquired interventricular septal defect is grave. Of the eighteen cases collected by Peirce,[10] ten patients were dead in fifteen days. If they withstand the trauma and the overload of the right heart, they may survive. Some patients have been followed as long as eleven years.[15] With the advance of cardiac surgery and the perfection of extracorporeal circulation equipment, early diagnosis and repair may save these patients.

Case Histories

Case 1. E. G., a sixty year old Caucasian woman was admitted to the hospital with sudden onset of crushing substernal chest pain. The patient had known severe hypertension of many years' duration and congestive heart failure had developed prior to this admission.

On admission the patient appeared acutely ill with a pulse of 64 and blood pressure of 180/90 mm. Hg. Her lungs were clear. The heart sounds were of poor quality and a grade 3 systolic murmur without a thrill was heard at the base.

The electrocardiogram showed evidence of an acute posterior myocardial infarction. Hemoglobin was 13.0 gm. per cent, white blood cell count 21,800 per cu. mm. with 85 per cent neutrophiles of which 20 per cent were stab forms.

Course: The blood pressure was maintained at hypertensive levels and the patient felt well until four days after admission when pleuritic chest pain and epigastric pain developed. It was suspected that pulmonary infarction had developed and she was given anticoagulants. X-ray and physical findings two days later supported the findings of pulmonary infarction. Eight days after admission signs of venous distention and hepatomegaly developed and the patient was maintained on anticoagulants

TABLE I
Catheterization Data: Postmyocardial Infarction Interventricular Septal Defect

Author	Pressures (mm. Hg)			O_2 Saturation (vol. %)		Flow (L./min.)		Left to Right Shunt (L./min.)
	RV	PA	PPA	RA	RV	Systemic	Pulmonary	
Muller, 1950[18]	85/?	85/?		10.19	13.6	5.8	11.0	5.2
Gottesagen, 1957[12]	90/−8	100/17	42/40	18.75	11.3	3.5	6.65	3.15
Shickman, 1959[19]	69/9			(53.9%)*	(87%)*			
Case 1	74/10	72/22	28/25	5.7	9.4	1.8	4.0	2.2

* Per cent saturation; no other data available.

and digitalized. Nine days after admission a grade 4 systolic murmur developed over and to the left of the sternum in the fourth intercostal space, with an associated faint systolic thrill. The diagnosis was made of a perforated ventricular septum. The blood pressure continued at over 100 mm. Hg systolic and heart failure did not increase. The patient was quite agitated and refused to maintain complete bedrest.

Catheterization and Operative Findings: On the fourteenth hospital day, the patient had a right heart catheterization (Table 1). The findings confirmed the interventricular septal defect. Pulmonary wedge pulse curves suggested an associated mitral insufficiency and left and right heart failure. The following day the patient's condition deteriorated and emergency cardiac surgery, using a closed technic, was attempted. At surgery the previous findings were confirmed. With a finger in the right ventricle, palpation revealed several adjacent defects in the mid-posterior part of the septum. The defects were closed and the pressures and oxygen saturations returned to normal. Pressures measured directly from the right ventricle prior to closure were 72/10 mm. Hg and immediately after closure were 30/10 mm. Hg. Unfortunately, the friable myocardium could not hold and the septum tore again, and bleeding could not be controlled. Ventricular fibrillation developed without successful resuscitation and the patient died on the table. No postmortem examination was granted.

Comment: The patient's history contained many well documented etiologic factors discussed previously as possibly contributing to rupture of the myocardium: (1) hypertension; (2) no previous coronary occlusion; (3) anticoagulation; (4) continuous physical exertion. The faint intensity of the systolic thrill could possibly be related to the position of the perforation in the posterior part of the septum. As stated previously, perforation is less frequent in the middle and posterior portions of the septum.

CASE 2. V. H., a nineteen year old Caucasian man, was in good health and had passed a high school physical examination to participate in football and a recent physical examination for employment. On June 27 he was in an automobile accident in which he was thrown against the dashboard and rendered unconscious. He was hospitalized and examination at that time revealed no fractures. On July 1, severe respiratory distress suddenly developed with a heart rate of 160, and he became cyanotic. At this time a very loud systolic murmur was heard along the left sternal border. Severe pulmonary edema occurred, necessitating treatment with a tracheotomy, digitalis and diuretics. Following this he gradually improved. Electrocardiograms on July 1 and thereafter showed an anteroseptal myocardial infarction. He was ambulatory for two weeks without dyspnea, cyanosis, or edema. Cardiac catheterization was advised because x-ray films of the chest had revealed progressive cardiac enlargement and persistent pulmonary vascular engorgement. He was admitted to the hospital for catheterization on August 27.

Physical examination revealed the patient to be well developed and well nourished. There was a left parasternal heave. The apical beat was in the fourth left intercostal space, 11 cm. from the mid-sternal line and 1 cm. lateral to the mid-clavicular line. There was a grade 3 systolic thrill maximal at the third left intercostal space next to the sternum. The thrill was also palpable at the left second and fourth intercostal spaces and less so at the apex. The anterior border of cardiac dullness was percussed 11 cm. from the mid-sternal line and 1 cm. lateral to the mid-clavicular line in the fourth left intercostal space. There was a grade 4 harsh pansystolic murmur heard best at the third left intercostal space. The murmur radiated over the entire precordium. A third, ventricular filling, sound was audible at the apex. There appeared to be a very short, early faint diastolic murmur at the third left intercostal space. P_2 was louder than A_2 and was not split. The blood pressure was 115/70 mm. Hg and the pulse rate was 90/minute with regular rhythm.

TABLE II
Catheterization Data: Post-traumatic Interventricular Septal Defect

	Pressures (mm. Hg)			O_2 Saturation (vol. %)		Flow (L./min.)		Left to Right Shunt (L./min.)
	RV	PV	PPA	RA	RV	Systemic	Pulmonary	
Guilford, 1953[11]	27/6	27/5	—	12.5	14.9	—	—	—
De Witte, 1957[16]	72/4	68/23	35/15	10.3	12.2	4.7	13.6	8.9
Cary I, 1958[17]	30/5	30/14	—	16.64	17.70	10.0	13.2	3.2
Cary II, 1958[17]	18/6	18/12	—	13.73	15.56	—	—	—
Cary III, 1958[17]	50/5	56/12	—	10.85	17.89	3.8	17.1	13.3
Inkley, 1958[9]	30/0	30/15	—	11.7	14.0	4.4	7.3	2.9
Peirce, 1958[10]	35/0	35/10	—	15.1	17.6	5.4	14.8	9.4
Case 2	74/12	66/27	18/13	12.5	15.8	6.4	16.8	10.4

The electrocardiogram showed findings of a typical anteroseptal myocardial infarct. The chest films showed moderate cardiac enlargement with an increase in the pulmonary vascular shadows indicative of increased pulmonary flow.

Catheterization and Operative Findings: The catheterization data are tabulated in Table II. The patient was then submitted to open cardiac surgery in November. Multiple perforations of the anterior septum adjacent to the left ventricular wall were found and closed by sutures but the patient still had a systolic thrill and murmur postoperatively. The patient has not been recatheterized.

Comment: The electrocardiogram in this case demonstrated evidence of an anteroseptal infarction, locating the area of perforations. The question arises as to whether the patient suffered a traumatic occlusion of the coronary artery with complicating perforations of the septum or whether these were tears due to physical forces. Catheterization demonstrated pulmonary hypertension (66/27 mm. Hg in the pulmonary artery) and a left to right shunt of 10.4 L./minute which was not due to a single defect but to multiple small defects.

Hemodynamic Studies

The catheterization data in Tables I and II list the results found in the available literature. It is evident that definitive diagnosis of an interventricular septal defect can be made in the usual manner by the oxygen gradient between the right atrium and right ventricle. In those patients with pulmonary hypertension, it is probably related to increased flow through the lesser circulation. Because of the acute nature of the increased pulmonary flow there is insufficient time for any permanent vascular change and resultant increase in vascular resistance. The right ventricular pressure dropped at surgery from 72/10 to 30/10 mm. Hg in Case 1 immediately on closure of the defect. This indicated complete reversibility of the hypertension in the lesser circulation in this patient. Pressures in Case 2 were not measured at the time of surgery and the patient has not been recatheterized since surgery. It is noteworthy that in the cases of postmyocardial infarction septal defects (Table I) the shunt flows from left to right are about equal to the systemic blood flows which are as low as 1.8 L./minute, whereas in the post-traumatic cases (Table II) the left to right shunt flows are in some instances quite appreciable and the systemic flows are all over 3.8 L./minute. This is probably due to the younger age of such patients with no preceding coronary arteriosclerosis, without appreciable embarassment of the myocardial reserve by the trauma.

Whereas the degree of left to right shunt usually indicates the size of the defect, in patients with large shunts after coronary occlusion or nonpenetrating trauma there could be many small perforations or in the case of trauma to the chest wall, multiple lacerations.

Summary

1. Acquired interventricular septal defects have been discussed and two new cases presented.

2. In both cases the diagnosis was confirmed by cardiac catheterization and the presence of moderate pulmonary hypertension was observed.

3. The pulmonary hypertension, in the absence of congestive failure, appears to be related to the magnitude of left to right shunt

and therefore should be reversible by surgical correction of the defect.

4. The degree of the left to right shunt may indicate the size of the opening in the ventricular septum and is due to either single or multiple defects.

5. The shunt flows and cardiac outputs in postmyocardial infarction septal defects are lower than in the post-traumatic cases. This is most likely caused by pre-existing myocardial disease present in the postinfarction group.

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Myocardial Infarction Following Penetrating Wounds of the Heart

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TRAUMA TO THE HEART is becoming more common. In many instances the injury is a contusion. Lacerations and penetrating wounds are also frequent and have been the subjects of multiple reviews in recent years. However, little clinical data have been published regarding electrocardiographic changes following myocardial laceration unobscured by the artifacts secondary to thoracotomy or pericardial aspirations.

The following is a report of a young woman who suffered multiple stab wounds of the precordium with subsequent myocardial infarction. No exploration or aspiration was performed. Serial electrocardiograms were taken during the acute and convalescent phases of her illness. Re-evaluation after one year indicated no permanent heart disease as a result of the wounds.

CASE REPORT

On November 5, 1958 a forty-two year old white housewife entered Syracuse University Hospital for treatment of chest wounds. She had been in good health until three weeks prior to this admission when she suddenly became emotionally depressed. About one hour before admission to the hospital she drank two small bottles of tincture of iodine and then stabbed her left chest repeatedly with a kitchen knife with a four inch blade. She collapsed and was hospitalized within forty-five minutes of the injury with evidence of profuse external bleeding.

Family history indicated that her husband, father, two brothers and daughter were healthy; her mother had died at the age of sixty-three years from a heart attack. Two sisters, although alive, had experienced "nervous breakdowns." Past history was noncontributory. A detailed social history gave no indication of previous significant organic or emotional illness.

Upon arrival, she was stuporous and no blood pressure or pulse could be detected. Nine bleeding wounds of the left anterior chest, emphysema about the wounds and dullness with absence of breath sounds at the base of the left lung posteriorly were present. A gastric lavage was done and therapy with intravenous Dextran was begun. Within fifteen minutes, the blood pressure was between 90 to 100 mm. Hg systolic and 70 to 80 mm. Hg diastolic, and she was mentally clear. Additional Dextran was administered followed by whole blood. Within one hour the patient was well stabilized although venous bleeding persisted from the wounds in the chest. A chest film was taken (Fig. 1); the chest wounds were then sutured. Thoracentesis confirmed the diagnosis of hemopneumothorax; closed tube thoracostomy drainage was established at the second left anterior interspace and the eighth interspace in the left posterior axillary line; 900 cc. of bloody fluid were recovered promptly. She tolerated the procedure well and thereafter her blood pressure never fell below 95/60 mm. Hg and her pulse did not rise over 100 per minute. Four hours after admission a twelve-lead electrocardiogram was taken (Fig. 2). Within five hours of her admission, she had received 700 cc. of Dextran and 1000 cc. of whole blood.

Laboratory data on admission revealed hemoglobulin, of 12.3 gm.per cent; hematocrit was 37; white blood cell count was 12.300 with 69 per cent bands, 28 per cent lymphocytes and 3 per cent eosinophiles. Urinalysis was within normal limits. Seven hours after admission, her hemoglobin was 10.5 gm. per cent; hematocrit was 29.5. Another 500 cc. of whole blood was administered and 5 per cent dextrose in water given intravenously. Penicillin and streptomycin were administered intramuscularly; tetanus antitoxin was also given after a negative skin test. Twenty-four hours after admission drainage from the chest totaled 1300 cc. of bloody fluid and her blood replacement was 2000 cc.; there was dullness over the lower half of the left lung and subcutaneous emphysema extended over the left anterior and lateral chest. Her hemoglobin was 11 gm. per cent; hematocrit, 33. Vital signs remained unchanged. No venous distension, pulsus paradoxicus or adventitious heart sounds were identified. After the first three hospital days the patient remained afebrile; her subsequent hospital course was characterized by progressive gain in strength and subsidence of her

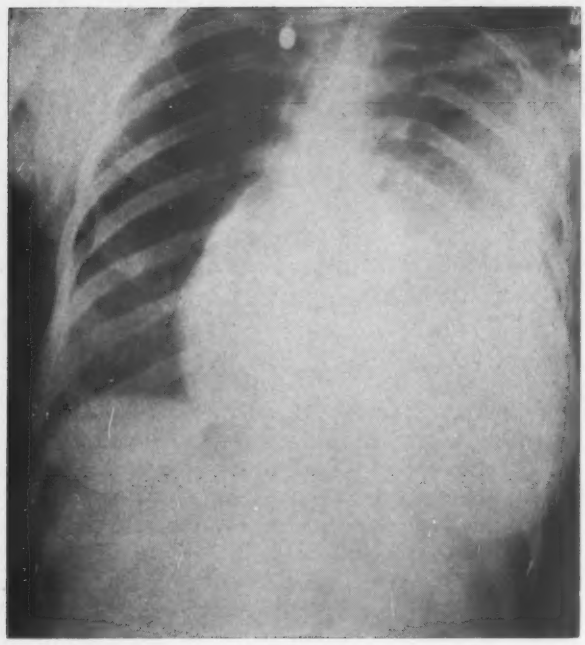

FIG. 1. Anteroposterior film of the chest soon after admission revealing evidence of changes in the left thorax consistent with a hemothorax. The left border of the cardiac silhouette is not discernible. An indwelling nasogastric tube is present.

emotional depression. The tubes in the chest were removed on November 7, 1958. On November 7, 1958 four sites of thoracentesis yielded no more fluid.

Penicillin and streptomycin were discontinued on November 9, 1958 and tetracycline was given orally; this was stopped on November 22, 1958. Repeated thoracenteses on November 27, 1958 and December 1, 1958 yielded a total of 750 cc. of serosanguinous sterile fluid.

Serial electrocardiograms were taken (Fig. 2). These were interpreted as indicating recent anterolateral myocardial infarction with gradual evolution of the process. Because of these findings, the patient was kept in bed for one month. Anticoagulants were not administered. She did not wear elastic stockings or bandages, but she was encouraged to move about freely in bed.

Spinal fluid examination on November 22, 1958, a gastrointestinal series on November 22, 1958 and a roentgenogram of the skull on November 24, 1958 revealed no abnormality. She was examined by a psychiatrist who considered her to have a schizoid reaction with depression. Out-patient psychiatric care was advised and she was discharged from the hospital on November 4, 1958.

She was examined on December 13, 1958, January 10, 1959, June 13, 1959 and November 22, 1959. On each occasion, physical examination, chest fluoroscopy and 12-lead electrocardiograms were taken. On each occasion the only objective evidence of her injuries was the multiple chest scars. On the study of November 22, 1959, metal clips were used to mark these scars and thereby to mark the site of knife wounds as they were anatomatically related to the intrathoracic structures (Fig. 3). In addition to the usual 12 leads of the electrocardiogram, additional unipolar leads were taken one interspace above and below the V_1–V_6 position. These are presented in Figure 2. On January 19, 1960 her two hours' postprandial blood sugar was 96 mg. per cent and the serum cholesterol was 202 mg. per cent.

COMMENTS

As Noth pointed out in 1946,[1] the lesion of the lacerated heart is unique. Specifically, it is like an infarct but is smaller, usually occurs in an otherwise normal heart and involves the right ventricle more than the left. To further obscure the pathology, pericarditis is always present. Coronary artery laceration may occur and shock, anemia and damage to the lung are not unusual. Multiple wounds are common.[2] The resultant damage depends upon the size of the wound, its character, direction, the chamber of the heart involved, associated coronary artery involvement and the area of confinement of the blood.[3] Each laceration is usually oblique. If the laceration extends to the lumen of the heart, the blood may clot; the thrombus organize; and a thin epicardial scar form. The main wound will often become lined with endothelium, forming an open false sacculated aneurysm.[4] It is not unusual for thrombosis to take place over the underlying injured endocardium; subsequent embolization or even complete filling of the right ventricle may occur.[5–6]

The bleeding, of course, does not always cease. The lacerated or perforated atria, probably because of their thin, poorly contracting walls, bleed more profusely than the thick, contracting ventricular walls.[4–7] If blood enters the pericardial sac more rapidly than it can leak through the small pericardial tear caused by the injuring weapon cardiac tamponade results.[8] The poorly distensible sac may become filled with blood. The rate of bleeding determines the clinical severity of the tamponade;[5] for example, the rapid introduction of 200 cc. of blood can be more disastrous than the slow accumulation of 500 cc. or more. Surprisingly small amounts of blood may be lost through large wounds; Hillsman[9] reported direct observation of ventricular bleeding in which a wound one-third inch in diameter spurted blood in systole, with only one teaspoon-

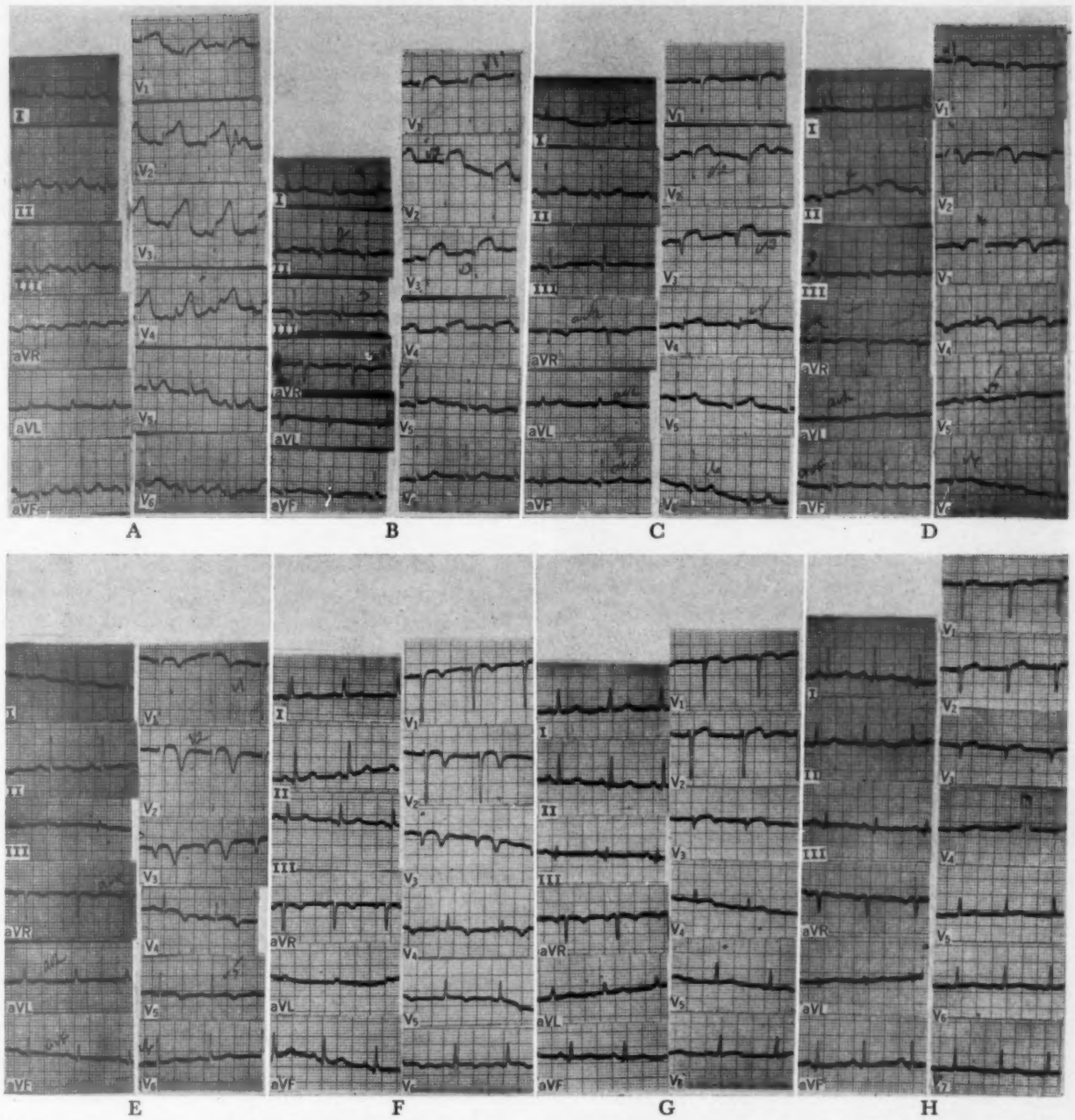

FIG. 2. Serial electrocardiograms taken at frequent intervals from the day of injury throughout the following year. In no record was there a disturbance of rhythm other than a rare ectopic ventricular beat. A, the initial record, taken on November 5, 1958 showed ST-T changes of recent anteroseptal injury and ischemia. B, taken on November 6, 1958; within twenty-four hours Q waves appeared in V_3 and V_4 and R in V_2 was smaller. C, taken on November 10, 1958; one week later there were Q waves in V_2–V_4, the S-T segments were returning toward the baseline and there was T wave coving in V_1–V_4. D, E and F show a return of the S-T segments to the baseline and progressive deepening of the T waves in V_1–V_6. Gradually these abnormalities are reversed. G, taken on June 12, 1959; the QRS complexes and S-T segments are normal; only minor T wave changes persisted in V_5–V_6. H, taken one year after the wounds were inflicted, November 22, 1959; the only abnormality is slight flattening of T waves in the left precordial leads.

ful per beat. Many authors report difficulty finding the lacerations when the sac is explored at surgery. If bleeding continues and the sac becomes filled with liquid blood the cardiac output and blood pressure fall.

In the present case it was clear that the patient had multiple deep wounds of the chest with left hemopneumothorax. Shortly after admission, it was realized that the myocardium was probably lacerated and attention was di-

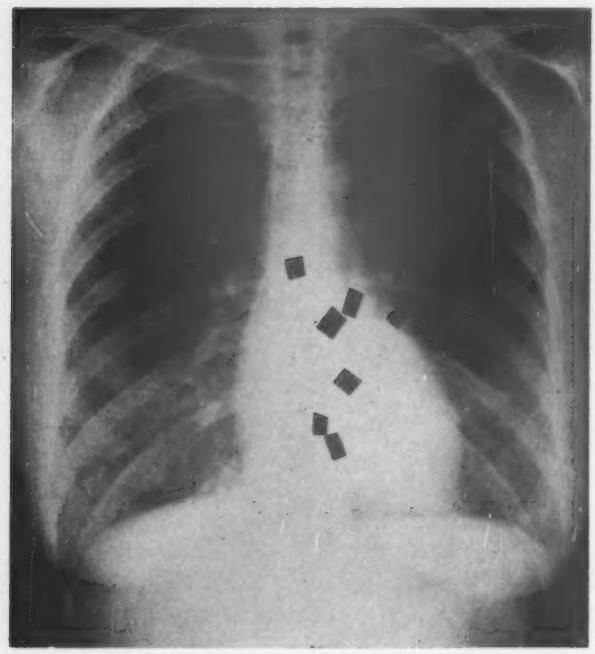

FIG. 3. Posteroanterior view of the chest one year later (November 22, 1959) discloses an essentially normal cardiac silhouette and lung fields. Also seen are nine superimposed markers placed on the anterior chest skin surface at the sites of the stab wounds.

rected to the probability of tamponade. Clinical observation never revealed evidence of increased intrapericardial pressure. Although fluoroscopy was not performed during the acute phase, repeated roentgenograms of the chest indicated only subcutaneous emphysema and left pneumothorax with effusion. As mentioned earlier, however, a considerable volume of blood can occupy the pericardium without clinical signs. We elected to continue conservative treatment and careful observation.

We did not believe it necessary to decompress the pericardium. Our gratifying result, we believe, was due to prompt restoration of blood volume by the use of Dextran and whole blood intravenously. It is unlikely that the elevation of venous pressure to overcome any abnormal caval-auricular gradient was of great importance here; such a beneficial factor, postulated by Cooper, Stead and Warren[10] and reaffirmed by Cooley et al.,[20] should be considered, however. We can not rule out the presence of a pericardial-pleural communication, a situation known to eliminate the possibility of tamponade.[11] However, a pericardial crunch was absent and there was no x-ray evidence of pneumopericardium. The probability, we believe, is that the anterior descending coronary artery or a major branch of this vessel was completely severed and promptly thrombosed. This is in keeping with the well-established surgical principle that a completely divided artery will bleed less than a partially severed artery that can neither retract or contract because it is held open by the remaining bridging segment. Such postulation is not necessarily contrary to the finding of Parmley et al.[12] that the nonpenetrating contused wounds of the heart with complete arterial rupture were followed by hemopericardium and tamponade rather than infarction.

To our knowledge, this case represents the first patient with a penetrating heart wound and subsequent myocardial infarction to be followed with serial electrocardiograms undistorted by surgical artifacts. Most data regarding the electrocardiogram in heart wounds appeared prior to World War II. The first recorded use of the standard leads was by Cole[13] in 1921. Davenport et al.[14] recorded on the CF_4 lead in 1935; in their patient the standard leads were taken prior to surgery and the same leads plus CF_4 taken after ligation of the anterior descending artery. The Q wave in CF_4 suggested infarction but interpretation was confused by the associated pericarditis. Similar data were next presented by Olin and Hughes[15] in 1940. In 1941, Solovay et al.[16] reviewed the literature of the electrocardiograms in heart wounds and attempted to correlate, for the first time, the three lead electrocardiogram with the site and extent of heart damage. Unfortunately, of the twenty-three cases studied one case had no early electrocardiogram and three had no late tracings. By present criteria pericarditis was usually present; but myocardial necrosis could not be identified.

The most comprehensive study of the problem was presented by Noth[1] in 1946. He reviewed 100 reported cases of heart wounds; seventy had electrocardiograms reproduced and available for his study. The analysis was difficult because of incomplete reports; brief operative descriptions and pericarditis which obscured other findings. The only conduction defect of diagnostic help was right bundle branch block which he considered to be diagnostic of right ventricular damage. Myocardial infarction was found early in only seven cases. In three of these it was accompanied by a diagnostic electrocardiogram; all cases had undergone surgical ligation of a coronary artery before the electrocardiograms were taken. The remaining four cases were "suggestive." Of all seven

cases only one had a precordial lead taken. Eight patients had electrocardiograms taken more than three months after the injury plus coronary ligation; three had normal standard limb lead records; four had an abnormal precordial lead and standard limb lead record and one had abnormal standard limb lead tracings but no precordial leads. Following this report, Kapp and Grishman[17] reported a gunshot wound of the heart with electrocardiographic data. Although the routine standard and unipolar leads were taken the patient was first studied one year after the injury. Excellent records were reported in 1952 by Beber and Limbeck;[18] twelve of fifteen records taken were published and included the standard leads and CF_1 to CF_6. The first records were taken two hours after surgery for a stab wound near the apex of the heart. The electrocardiograms had not returned to normal nine and one-half months later but the changes seemed to be those of pericarditis. Subsequently, Spencer and Kennedy[19] presented two cases, but the surgical aspects of the material were emphasized and the electrocardiograms were not published. They were reported to reveal "myocardial injury" and "a gradual return of serial electrocardiograms toward normal."

The electrocardiograms taken on this patient fulfill the generally accepted criteria of recent myocardial infarction with gradual evolution over a period of one year to normal. These changes are those expected when the continuity of the channel of the anterior descending coronary artery or a major branch thereof is lost. As mentioned earlier regarding the absence of detectable tamponade, we suspect that the vessel was completely severed. Multiple lacerations of one or more vessels cannot be excluded or can the possibility that pre-existing arterial disease plus shock led to intraluminal thrombosis and infarction. It is possible that the contused or lacerated artery will not thrombose unless it was diseased before trauma.[12]

Summary

A case is reported in which a presumably normal heart was injured by self-inflicted penetrating wounds of the chest. No tamponade was identified although extensive blood loss occurred.

Electrocardiographic evidence of a recent myocardial infarct followed the injury and electrocardiograms are available, unaltered by surgical manipulations, from early in the illness throughout the following year. The patient exhibited no further complications of the conservatively treated penetrating heart wounds.

It is postulated that a coronary artery was completely severed leading to myocardial infarction but not to extensive intrapericardial bleeding.

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Myocardial Infarction Following Steroid Therapy in Periarteritis Nodosa*

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PERIARTERITIS NODOSA was originally described in 1866 by Kussmaul and Maier. Since that time numerous reports have stressed the multisystem involvement with its concomitant bizarre clinical picture. Myocardial involvement due to lesions of the coronary vessels has been previously demonstrated in postmortem examinations.[1] The coronary vessels rank next to the renal vessels in frequency of involvement.[2] Despite this fact, clinically evident antemortem myocardial infarction has been infrequently reported in patients with periarteritis nodosa. This relative infrequency has been explained on the basis that damage to the coronary vessel occurs slowly, allowing ample time for collateral development.[3] The following is a case of a patient with periarteritis nodosa with a clinically silent myocardial infarction developing shortly after a course of steroid treatment.

CASE REPORT

A thirty-four year old white man was admitted to the U. S. Naval Hospital on August 20, 1959 for migratory polyarthralgia of approximately twelve days' duration. He was in apparent good health until July 27, 1959 when a sore throat developed and he was subsequently treated for three days with sulfa drugs. He responded well and three days after this treatment he received a typhoid, diphtheria-pertussis-tetanus and smallpox inoculation preparatory to a sea voyage. Approximately two weeks later he first noted the onset of posterior cervical discomfort and myalgia in addition to migratory arthralgia involving the elbows, knees and metacarpophalangeal joints. He was admitted to a dispensary and noted to be in moderate distress due to severe pain in the joints. The tonsillar pillars and uvula were markedly erythematous and tender. There were expiratory wheezes over the lung bases. Blood count revealed a leukocytosis of 17,000 per cu. mm.; an electrocardiogram revealed no abnormalities. He was treated with bed rest and salicylates; however, because of the progressive character of his illness he was transferred to the Naval Hospital at Newport, Rhode Island.

Physical Examination: The patient appeared toxic and febrile with a temperature of 101°F. The blood pressure was 138/104 mm. Hg in both arms. The patient was chronically hoarse, speaking with slightly more than a rasping whisper. There was an ulcerated patch over the uvula and the tonsils and pharynx were markedly injected. There were diffuse wheezes over the lung fields. The heart was within normal limits. There was diffuse swelling of the soft tissues of the hands and feet with moderate pain produced on motion of the ankles and knees. The joints themselves were not swollen or erythematous. No rash was noted.

Laboratory Data: The white blood count was 15,200 per cu. mm. The sedimentation rate was 35 mm. hour (Wintrobe). The results of the following studies were within normal limits: hemoglobin and hematocrit, urinalysis, urinary porphyrins, serum electrolytes, serologic test for syphilis, blood urea nitrogen, total serum protein, liver function studies including bromsulphalein excretion, lumbar puncture studies, bone marrow aspiration, latex agglutination, hemostatic function tests, febrile agglutinations, rickettsial agglutinations, six blood cultures, cultures of the throat, skin, and sputum, coccidiodin skin test and nine lupus erythematosus preparation examinations. Test for C-reactive protein on admission was positive. The antistreptolycin O titer was 300 to 400 Todd units. Histoplasmin skin test was 3 plus. Purified protein derivative #1 was 4 plus. The trichinella skin test was negative. Urinary studies in the later stages of hospitalization revealed increased numbers of white cells and red cells in the sediment. Creatinine clearance on September 1, 1959 was 85 L. for twenty-four hours. Serum protein electrophoresis revealed a decreased albumin with marked increase of the alpha-1 and alpha-2 globulins. Serum cryoglobulins and macroglobulins were not present.

Hospital Course: The hospital course was stormy

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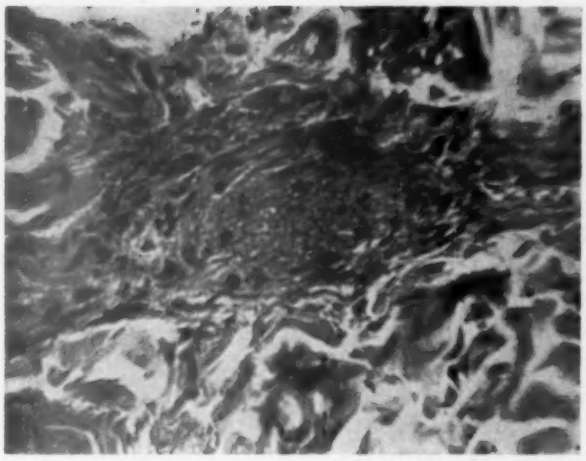

FIG. 1. Necrotizing angiitis of a cutaneous artery. The wall of the vessel is partially replaced by necrotic debris. The lumen is obliterated by a thrombus composed of fibrinoid material. (Hematoxylin and eosin stain; original magnification × 85.)

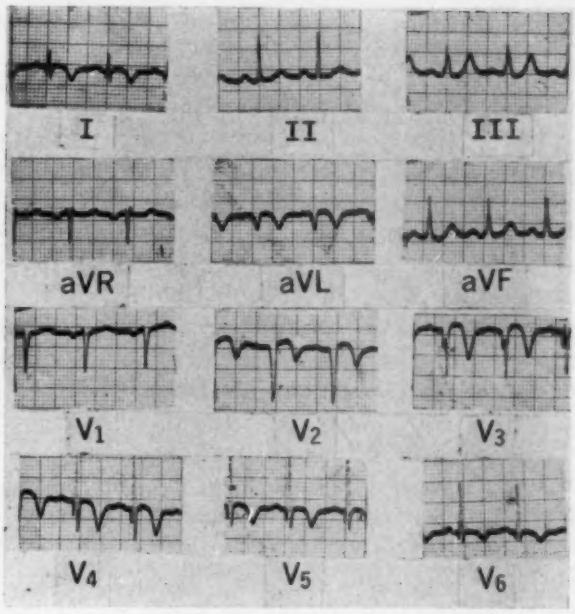

FIG. 2. Electrocardiogram showing recent infarction in the anterolateral left ventricular wall.

and complicated, characterized by multiple system involvement. Initially the patient was febrile and toxic; on the fifth hospital day erythema multiforme developed. Shortly thereafter he complained of excruciating muscle pain. Subsequent examination revealed diffuse muscle tenderness associated with a leukocytosis of 40,000 per cu. mm. Large doses of salicylates were then administered and in a period of forty-eight hours the patient showed marked improvement. On the tenth hospital day bilateral median nerve neuropathy developed. Concomitantly, a black ulcerative eschar appeared over the right lateral malleolus. On the twentieth hospital day there was marked blanching of the left lower extremity with moderate diminution of the peripheral arterial pulsations and the skin temperature. This was interpreted as an acute arteriospastic episode. A biopsy of the muscle from the right calf revealed waxy degenerative changes of the muscle fibers; however, no acute inflammatory processes were seen. A punch biopsy of skin adjacent to the ulcerative eschar over the right lateral malleolus revealed necrotizing arteritis of the smaller arteries, some of which were occluded by fibrinoid material (Fig. 1). A biopsy of the vocal cord revealed chronic inflammation with focal areas of fibrinoid necrosis of the connective tissue. The patient was then given prednisone, 60 mg. daily, continued in gradually decreasing amounts for twenty-one days. One week following the onset of steroid therapy acute left orchitis developed associated with a marked leukocytosis with white blood counts ranging up to 40,000 per cu. mm. The acute process gradually subsided and in subsequent weeks the left testicle became completely atrophic.

Throughout the early stages of hospitalization serial electrocardiograms were taken at weekly intervals. All of these were within normal limits.

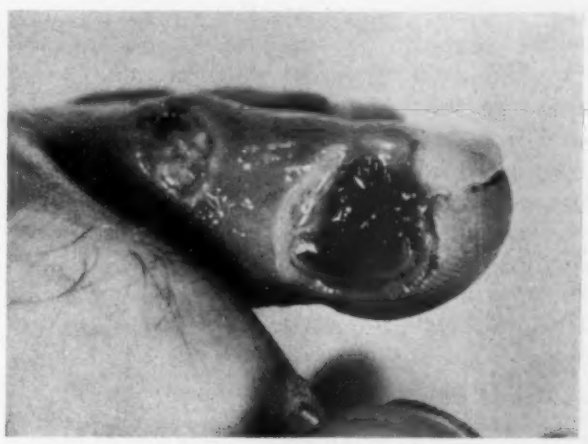

FIG. 3. Necrotic ulcerations (skin infarcts) of the medial surface of the second toe of the right foot.

On November 10, 1959, ten days following the withdrawal of steroids, a routine serial electrocardiogram, revealed evidence of a recent anterolateral myocardial infarction (Fig. 2). In retrospect, the patient could recall no episodes of pain in the anterior chest antedating these findings. Further serial electrocardiograms revealed the evolution of an anterolateral myocardial infarction, from which the patient made an uneventful recovery. The remainder of the hospitalization was complicated by recurrent necrotic ulcerations of the toes (Fig. 3). These were interpreted as being secondary to obliterative angiitis of the smaller arteries of the skin. When last seen, his ability to walk was moderately curtailed due to recurrent ulcers of the toes. The cardiac and renal

status remained adequate and hypertension was minimal, in the vicinity of 150/90 mm. Hg.

Comments

The multisystem character of this patient's disease fits well with the previously recorded features of periarteritis nodosa.[2-5] Diffuse myalgia and arthralgia, erythema multiforme, peripheral neuropathy, acute orchitis, myocardial infarction and chronic indolent necrotic ulcerations of skin all appeared during various phases of his illness. On the other hand, overt nephritis with hypertension has not yet appeared. The biopsy demonstration of necrotizing angiitis associated with the aforementioned clinical features justified the antemortem diagnosis of periarteritis nodosa.

The history of exposure to sulfonamides and vaccines approximately three weeks before the apparent onset of the disease raises speculation regarding classification and etiology. Zeek[6] originally classified necrotizing angiitis into five major groups as follows: (1) hypersensitivity angiitis, (2) allergic granulomatous angiitis, (3) rheumatic arteritis, (4) periarteritis nodosa and (5) temporal arteritis. She contends that these conditions, although characterized by similar histopathologic changes, should not be considered as one pathologic entity.[7] As is true with many such cases, some features of this patient's illness fit both with hypersensitivity angiitis and periarteritis nodosa. However, the general course, duration and histopathologic changes best fit into the periarteritis group. Some recent authors have believed that for practical purposes differentiation of the hypersensitivity angiitis and periarteritis nodosa groups are not warranted as these types are probably variations of the same disease process.[8,9]

One of the more unusual and troublesome features of the present case has been the chronic recurrent necrotic ulcerations of the toes. Skin lesions of periarteritis nodosa can assume various manifestations from neurodermatitis, purpura hemorrhagica and skin nodules[3] to frank gangrene.[10]

As is true in many diseases of obscure etiology and pathogenesis, steroids have been administered to patients with periarteritis nodosa with varying degrees of success. The role of steroids in general in the so-called collagen vascular disease group has never been fully clarified. In fact, there is sporadic evidence in the literature which indicates that steroids may be distinctly harmful in some of the collagen vascular diseases.[2,11] Cases have been reported with disseminated lupus in which flagrant lesions of classic periarteritis nodosa have developed after steroid therapy.[7] Reports have incriminated steroids in the acceleration of advanced renal disease in scleroderma.[12] Taubenhaus et al.[2] reported a fatal endarteritis developing in a patient with chronic rheumatoid arthritis during treatment with cortisone. A recent study in England, utilizing retrospective technics, attempted to assay the role of cortisone in patients with periarteritis nodosa.[13] Although the incidence of hypertension was greater in the control group no real difference in duration of survival was revealed in the treated as compared to the untreated group.

The development of a silent myocardial infarction in our patient shortly following steroid administration suggests some exaggerated effects upon the coronary arterial tree. Baggenstoss et al.[14] reported the postmortem findings of two patients with periarteritis nodosa who received extensive steroid treatment. They noted that most of the involved arteries revealed evidence of marked healing with very little acute or active inflammation noted. Unfortunately, however, in the process of healing fibrous obliteration of the lumina of the vessels occurred resulting in infarcts in many organs. In our case, it is possible that similar events occurred with the major damage silently following the steroid-induced fibrous obliteration of the lumen of a major coronary vessel. Interestingly enough, the acute orchitis developed following the administration of steroids. Similar observations have been previously made regarding acute orchitis in periarteritis nodosa after administration of steroids.[15] The foregoing evidence seems to indicate that at least in some patients with periarteritis nodosa, steroids, despite their antiphlogistic effect, may actually hasten damage to organs by accelerating obliteration of the vascular pathways.

Summary

A case of periarteritis nodosa in a thirty-four year old white man is presented. A clinically silent myocardial infarction developed following steroid treatment. Some of the potential dangers of steroids in this disease are briefly discussed.

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Myxedema Heart Disease and Rheumatic Heart Disease*

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RHEUMATIC heart disease and thyrotoxicosis frequently coexist; however, rheumatic heart disease and spontaneously occurring myxedema are rarely found in the same patient. Hypothetically, patients having high blood lipids (pregnancy, diabetes, hypothyroidism, nephrosis) are most refractory to rheumatic fever,[1] and by inference, rheumatic fever developing in the presence of myxedema is a rare condition. A survey of the literature of the last ten years fails to reveal any report of the combined diseases, regardless of their order of appearance. Another reason why these two conditions are not seen together more often is the rarity of myxedema in the younger age group in which rheumatic heart disease is most frequently seen. The following case report represents myxedema heart disease developing in a patient with rheumatic valvular disease.

CASE REPORT

A thirty-six year old Polish housewife was admitted to St. Luke's Hospital on April 23, 1950. For six months she had noticed increasing weakness, apathy, difficult breathing, swelling of the face and tongue and puffiness about the eyes. Four months prior to the admission she had had a miscarriage. For two to three months she had noticed drying of the skin and scalp, loss of libido, aversion to cold and excessive loss of hair. She developed a halting and indistinct speech. Her memory became hazy. One month before admission she had been given a transfusion at another hospital for "anemia." She had become very tired and upon admission could sit up in bed only with great effort. There was no orthopnea, angina, swelling of the ankles or paroxysmal nocturnal dyspnea.

At eight years of age she had vague joint pains and was put to bed for a few weeks with the diagnosis of "acute rheumatic fever." About this time a school physician remarked that her heart was enlarged. She was well until the age of eighteen when she had the first of a series of "heart palpitations." She describes a total of five paroxysms of tachycardia. The last paroxysm was in 1947 and required hospitalization for a week. The heart rate was 180 and the basal metabolism was normal. At this time she was employed as a cashier and was able to make change quickly. Later in 1947 she developed difficulty in swallowing and a choking sensation. Her thyroid gland enlarged and she was given Lugol's solution. She took this medication until the onset of her present illness.

Physical examination on the present admission showed a well developed, obese, white female lying flat in bed. She weighed 158 pounds. Her speech was slurred, halting and slow. Talking or moving required great effort and caused fatigue and shortness of breath, which was not relieved by an upright position. Her face was puffy, particularly the lower eyelids. The skin was cold, dry and coarse. The hair and scalp were dry. The thyroid was firm, regularly enlarged and nontender. The lungs were clear to percussion and auscultation. The liver edge was palpable. There was neither peripheral nor presacral edema. The pulse was regular, slow and 62 beats per minute. Blood pressure was 124/76 mm. Hg. The heart was enlarged to the midaxillary line. There was a blowing, grade 3 crescendo systolic murmur and a grade 2 diastolic murmur heard loudest over the base of the heart. A grade 2 higher pitched, prolonged crescendo systolic murmur was heard at the apex and transmitted toward the axilla. The first apical heart sound was overactive.

Teleoroentgenogram of the chest (Fig. 1A) showed the transverse diameter of the heart to measure 19.5 cm., representing an increase over 25 per cent of the expected average according to the chart of Ungerleider and Clark.[2] The left border of the heart extended to the lateral thoracic wall and completely obliterated the left costrophrenic angle. Fluoroscopically, cardiac pulsations were shallow, and the presence of pericardial fluid could not be excluded. In the right anterior oblique projection, the esophagus was displaced posteriorly in the region of the left

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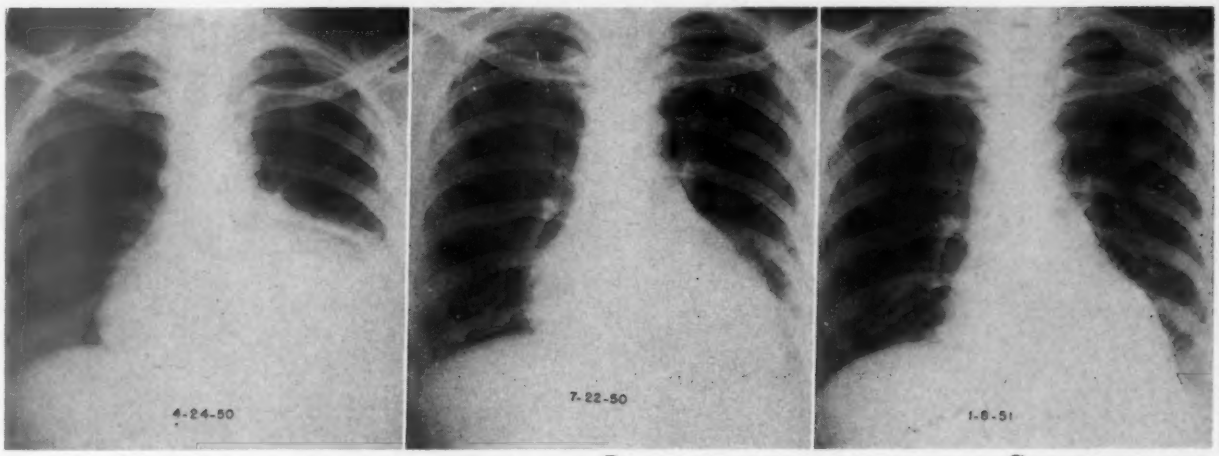
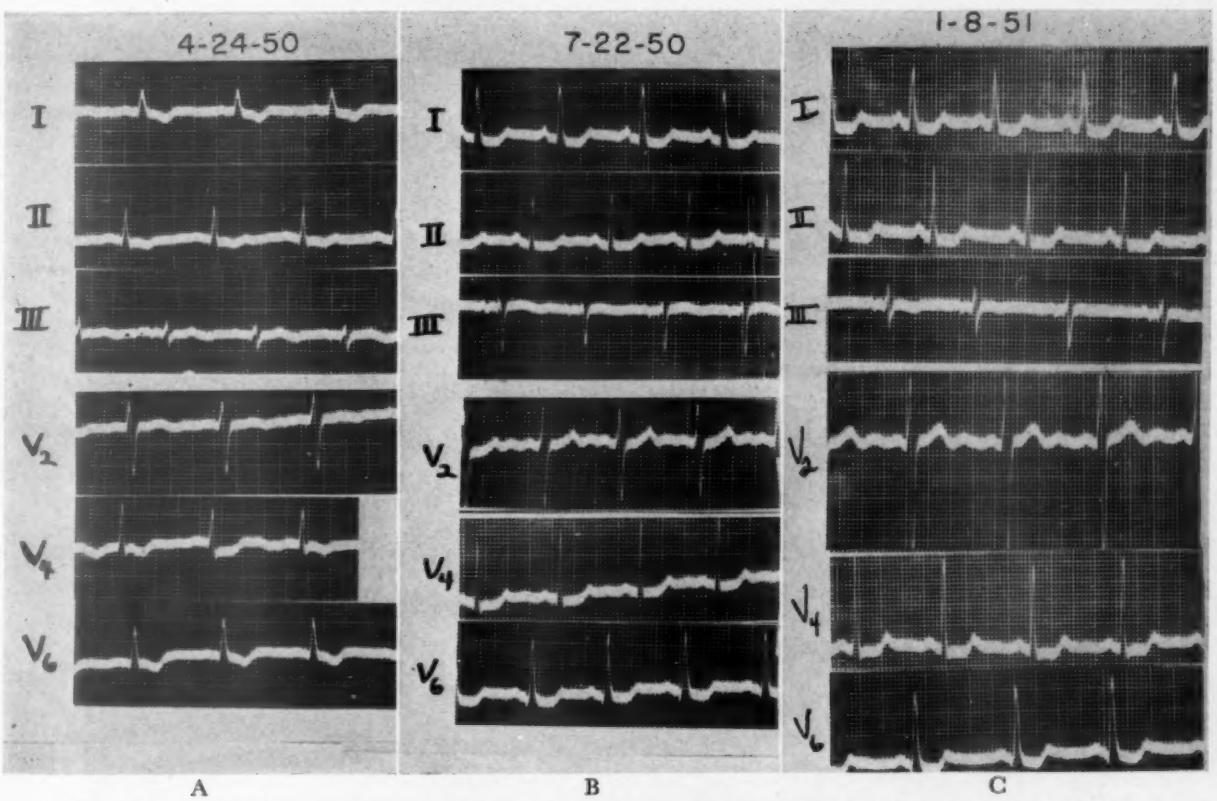


A B C

FIG. 1. A to C, chest x-rays showing decreasing heart size following administration of thyroid. Therapy was started about May 1, 1950.



A B C

Fig. 2. A to C, electrocardiograms of same dates as x-ray films in Figure 1. Note increasing voltage.

atrium. It was believed that both ventricles were enlarged.

Pericardial taps were attempted in the fourth and fifth interspaces medial to the anterior axillary line. No fluid was obtained.

The electrocardiogram on admission (Fig. 2A) showed the T waves to be negative in leads I, II, V_4 and V_6. The height of the QRS complexes was only slightly diminished, measuring 7.5 mm. in lead II.

Significant laboratory data showed the basal metabolic rate to be minus 40 per cent (Wetzel standard). The blood cholesterol was 250 mg. per cent. Red blood cells numbered 3.6 million/cu. mm., hemoglobin 11.4 gm. per cent, and hematocrit 33 per cent. There were 7,800 white blood cells per cu. mm., differential was normal.

Clinical Course: The patient was given iron sulfate 0.3 gm. three times a day and thyroid extract, 15 mg. twice a day. After eight days the thyroid dosage was increased to 30 mg. twice a day. Digitalis,

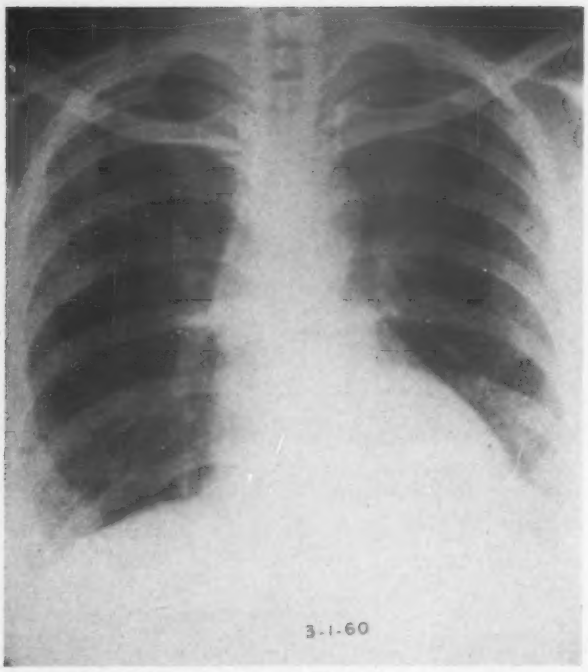


FIG. 3A. Chest x-ray film after ten years.

which had been given to the patient for several months prior to admission, was continued. Within a few days dramatic changes were noticed. Her lethargy, slow speech and shortness of breath disappeared in one week. During the second week she was walking from room to room. In three weeks she had lost fourteen pounds and was eager to leave the hospital and return to work.

After three months the basal metabolic rate had risen to 0. The cholesterol was 181 mg. per cent. Red blood cells numbered 4.55 million/cu. mm. and the hemoglobin was 13.9 gm. per cent. The transverse cardiac diameter decreased to a measurement of 15 cm. (Fig. 1B). The voltage of the QRS complex in lead II increased to 12 mm., the mean axis remaining the same (Fig. 2B). Seven months later the heart size had decreased further (Fig. 1C) and the QRS voltage was taller, measuring 16 mm. in lead II (Fig. 2C).

Since the initial hospitalization she has been asymptomatic. She has carried on all of her normal household activities. In October 1959 she weighed 175 pounds. The basal metabolic rate was plus 5 per cent, cholesterol 223 per cent and hemoglobin 14.8 gm. per cent. The heart was only slightly enlarged and the voltage of QRS in lead II was 16 mm. (Fig. 3). The T waves were also taller and upright. The heart murmurs have remained essentially unchanged (Fig. 4), indicating the presence of aortic stenosis and insufficiency and mitral insufficiency.

COMMENTS

This case seems to fulfill Zondek's[3] criteria for the diagnosis of hypothyroid heart disease,

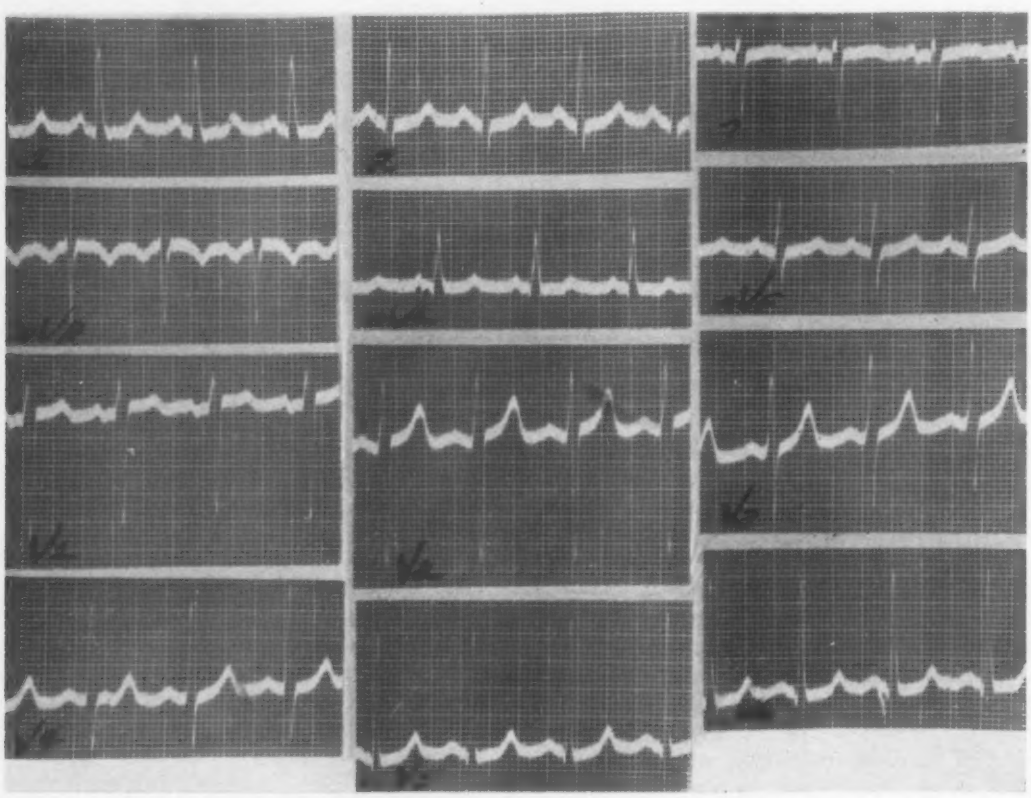


FIG. 3B. Electrocardiogram after ten years.

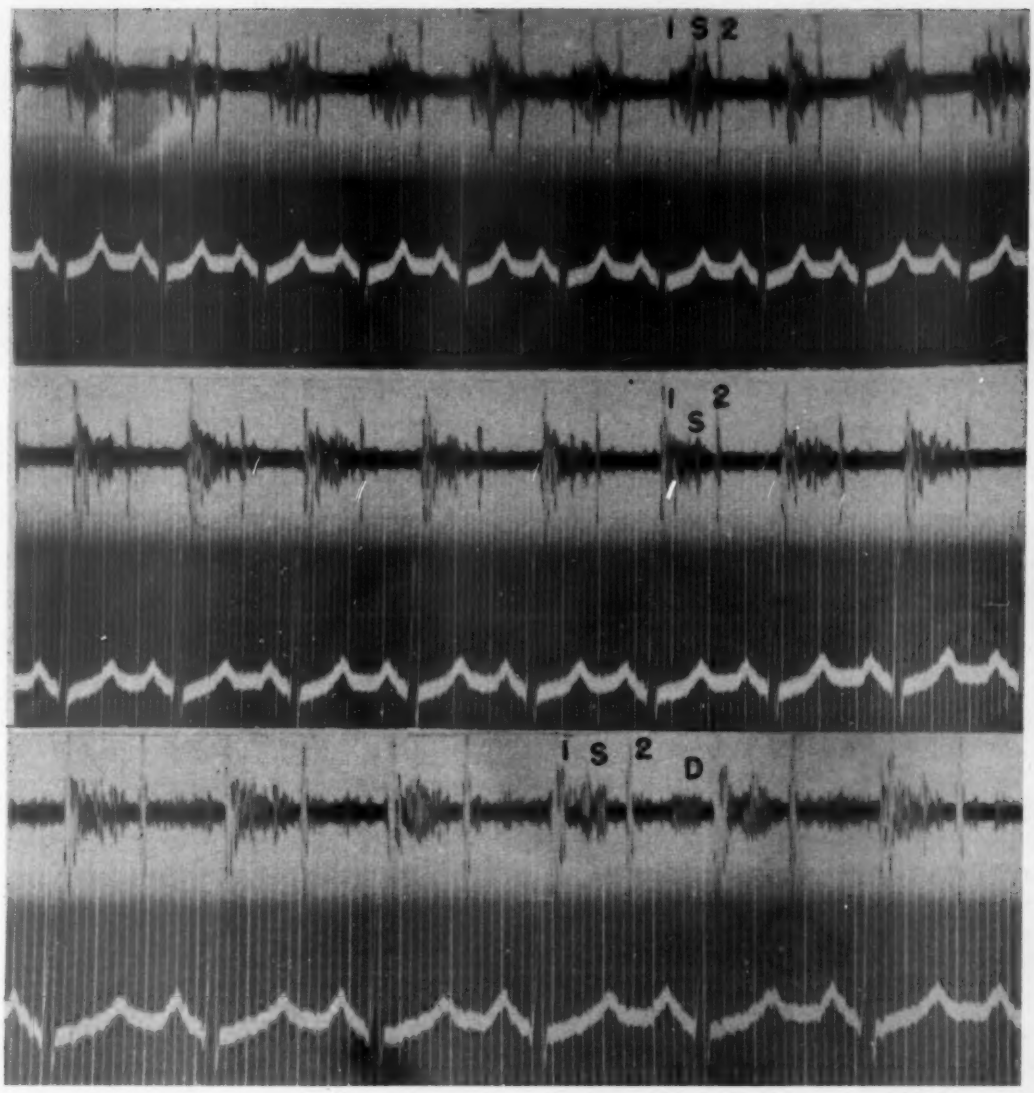


FIG. 4. Phonocardiograms taken March 1, 1960. Top record at aortic area shows the rough systolic murmur of aortic stenosis. The middle record taken at the apex reveals the decrescendo systolic murmur of mitral insufficiency. The bottom tracing was taken at the third left parasternal interspace. Increased amplification was used here to demonstrate the diastolic murmur of aortic insufficiency. (These recordings were made by Drs. C. Zegiob and E. Riff.)

i.e., dilatation of the heart, slow indolent heart action and low complexes in the electrocardiogram. The type of failure corresponds to that in myxedema heart disease first described by Fahr.[4] In this case myxedema is believed to have developed following the illness described in 1947, which could well have been thyroiditis.

Ellis et al.[5] became interested in the mechanism of cardiac failure in myxedema heart disease. They showed that blood flow is apparently decreased out of proportion to the lowered oxygen needs of the body. This fact, plus the obvious cardiac enlargement and electrocardiographic changes, seemed to them evidence of heart damage and circulatory insufficiency. It is probable that the cardiac enlargement is due partly to this increased proportionate oxygen demand, and partly to the increased bulk due to the myxedematous state affecting the heart tissues.

In this patient all routine measures for the control of congestive heart failure, under the assumption that it was due to rheumatic heart disease, had been unsuccessful. With the dramatic changes effected by the administration of thyroid hormone, there is little doubt as to the cause of her failure. McGavack et al.[6] have emphasized the importance of the smallness of the thyroid dosage to be used in initial treatment. Even in the absence of angina

pectoris, the increased metabolic rate and blood flow brought on by return to normalcy might precipitate angina pectoris. Sudden death may occur just when the myxedema itself is under control. We encountered no anginal pain in this patient.

Today, nearly ten years after her first hospital admission, she is still taking 1 gr. (60 mg.) of thyroid extract per day. Digitalis has been discontinued. In view of the asymptomatic period, it is apparent that the valvular disease has as yet been of little physiologic consequence. It did serve to confuse the picture in the initial stages.

Summary

A case of myxedema heart disease developing in a person with valvular damage of rheumatic origin has been presented.

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Pelvic Vein Thrombosis with Pulmonary Vascular Lesions Simulating Primary Pulmonary Hypertension*

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THERE IS still a controversy as to the existence of primary pulmonary hypertension as a clinical entity. This has been heightened in recent years by the greater use of the technic of cardiac catheterization. The critical problem, in most instances, is the decision as to whether the pulmonary vascular changes are *secondary* to long-standing pulmonary hypertension of unknown etiology (so-called primary pulmonary hypertension) or are the *primary* disease leading to a secondary pulmonary hypertension.

McGuire et al.[1,2] have highlighted this problem by accepting the diagnosis of primary pulmonary hypertension only if the following criteria are met: (1) The demonstration of right ventricular hypertrophy in the absence of any other cardiac abnormality; (2) the demonstration, by cardiac catheterization, of an elevated pulmonary arterial pressure and of a normal pulmonary wedge pressure;† (3) the absence at necropsy of occlusive lesions in the pulmonary vascular tree, unless such lesions are so sparse that they could not possibly account for the hypertension in this circuit.

Brachfeld et al.[3] have indicated the necessity of performing left heart catheterization in patients with pulmonary hypertension and normal wedge pressure since the latter measurement, being subject to error and sometimes unobtainable, may contribute to the overlooking of an "occult mitral stenosis" which might be surgically corrected. They present three patients with pulmonary hypertension, two of whom had left heart catheterization. The one not having left heart catheterization was demonstrated at autopsy to have mitral valve disease. Of the other two patients, one had surgically correctable mitral stenosis and the other had a normal gradient across the mitral valve and was presumed to be a case of primary pulmonary hypertension. The latter patient died soon after catheterization; and necropsy showed intimal thickening in the pulmonary arterial tree and pinpoint lumina in many of the smaller vessels, so that this patient may not have fulfilled the third criterion of McGuire.

We are presenting a case that was considered to be one of primary pulmonary hypertension and in which both left and right heart catheterization were performed. The antemortem diagnosis had to be changed after autopsy because the findings of extensive pulmonary vascular changes and of thrombosis in the pelvic veins led to the diagnosis of multiple pulmonary embolization with secondary pulmonary hypertension as described by Owens et al.[4]

CASE REPORT

The patient, a thirty-seven year old white woman, entered the hospital in June 1957 because of swelling of the ankles and legs, large abdomen, easy fatigability and shortness of breath of about four months' duration.

Three years before she had a cyst removed from one ovary plus appendectomy. Simple mastectomy was performed one year prior to admission. The patient had otherwise enjoyed excellent health until about one year before admission, when she first experienced dizziness and choking sensation in the upper chest area and neck upon moderate physical exertion (walking). These complaints were transient and usually disappeared upon resting for a few minutes. There was no chest pain or palpitation.

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† This criterion does not seem valid because chronic pulmonary lesions causing secondary cor pulmonale would give the same data. It is acceptable only in the exclusion of mitral stenosis.

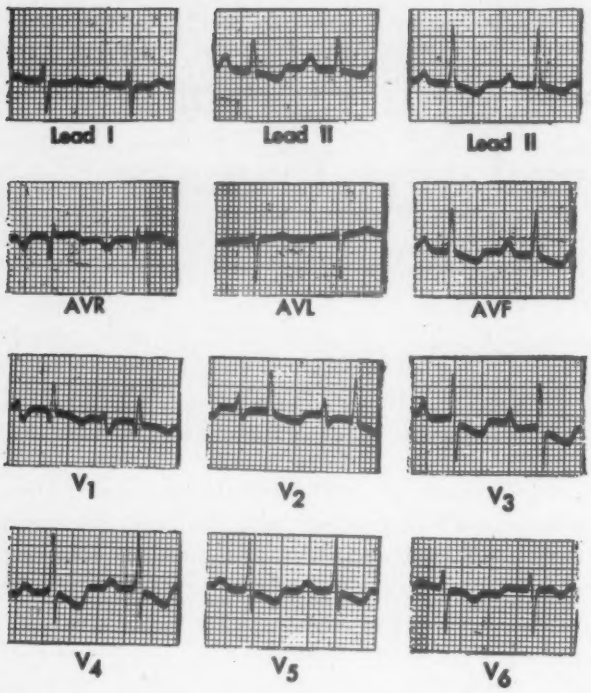


FIG. 1. Electrocardiogram. Note tall P_2; tall, diphasic P in V_2; right axis deviation; evidence of right ventricular hypertrophy and "strain."

Physical examination revealed a thin, frail woman in no acute distress. The neck veins were slightly distended and pulsating. There was no cyanosis. Blood pressure was 120/70 mm. Hg and pulse 100 per minute and regular. The heart was enlarged to the left on percussion; a grade 1 to 2 soft, blowing systolic murmur and a diastolic rumble were heard at the apex. P_2 was louder than A_2. The border of the liver was palpable two to three fingerbreadths below the right costal arch. There was moderate ankle edema. The patient was believed to have rheumatic heart disease with congestive heart failure.

The *laboratory data* were as follows: hemoglobin 14.6 gm. per cent, hematocrit 45 per cent, white blood cells 9,200 per cu. mm., blood urea nitrogen 13 mg. per cent, C-reactive protein negative, antistreptolysin O titer 12 units. Repeated blood cultures were negative.

Venous pressure was 230 mm. H_2O. Circulation time with sodium dehydrocholate was twenty-two seconds.

Two electrocardiograms (Fig. 1) taken a week apart were essentially similar, both showing right axis deviation, prominent R in V_2 and V_3 and T wave inversion in leads II, III, aVF and all precordial leads. The interpretation was right ventricular hypertrophy. The P wave duration exceeded 0.04 second in all leads. It revealed right atrial distention in lead V_2.

X-ray films (Fig. 3) showed an enlarged heart with slight prominence of the pulmonic conus. The barium-filled esophagus was not displaced but in lateral views, both ventricles seemed enlarged (Fig. 3).

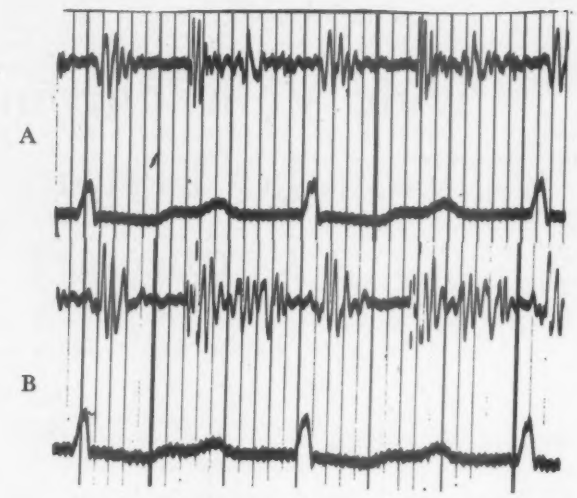


FIG. 2. Phonocardiograms. A, apex; B, apex, with patient in left lateral decubitus. Note diastolic gallop sound, which becomes a rumble in left lateral decubitus. Prolonged second sound.

Phonocardiogram showed minimal systolic vibrations over the apex. Diastolic vibrations at apex and midprecordium coincided with the third and fourth heart sounds (Fig. 2).

Left and right heart catheterization:

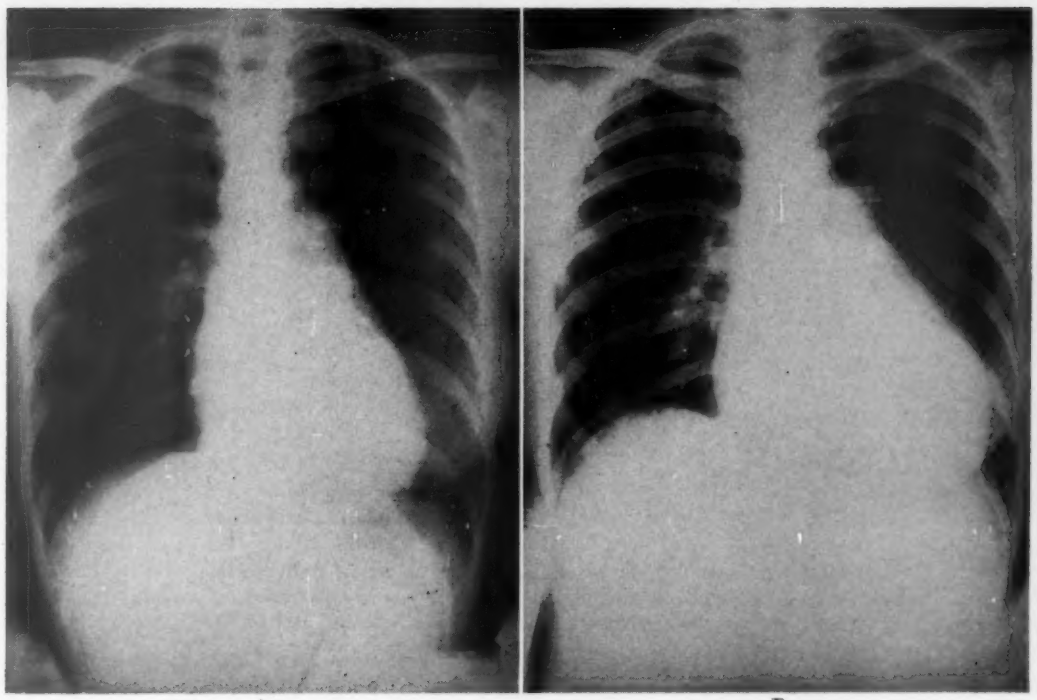
Pressures:
- Left atrial = 7 mm. Hg (mean)
- Left ventricle = 112/7 mm. Hg
- Right atrial = 13 mm. Hg
- Right ventricle = 100/13 mm. Hg
- Pulmonary artery = 100/50 mm. Hg (mean 66)
- Wedge = 4 to 7 mm. Hg

Cardiac output = 2.43 L./minute
Cardiac index = 1.67 L./minute
Pulmonary arteriolar resistance = 1940 dynes seconds cm^{-5}.
Predicted vital capacity = 3.1 L.
Observed total and three-second vital capacity = 2.7 L.
Oximetric study = negative for any shunts.
O_2 consumption = 204 cc./minute.
Arteriovenous O_2 difference = 8.4 vol. per cent.
Arterial blood oxygen saturation = 94 per cent.

The conclusion was severe pulmonary hypertension, right ventricular failure and no evidence of mitral valve disease.

Clinical Course

During the period of hospitalization the patient was placed on low salt diet, and was given digitalis and injections of mercurial diuretics. As a result, she lost 10 pounds and most of her peripheral edema. She was discharged feeling much improved.



A B

FIG. 3. Chest films. A, June, 1957. B, December, 1957. Note progressive enlargement of cardiac silhouette, fullness of pulmonary arch; clear lung fields with decreased vascular markings.

After about six months, the patient was readmitted to the hospital because of marked pedal edema, exertional dyspnea and orthopnea. During the period between hospitalizations, she continued to receive a low salt diet, digitalis and mercurial diuretics.

The physical findings at this time were similar to those of the previous admission but, in addition, she presented severe ascites and presacral edema. During the second hospitalization, various oral diuretics were given. Inasmuch as the disease appeared to be progressive, she was given an oral anticoagulant and prednisone.

For the next five months, the patient's status continued to deteriorate and the retention of fluid progressed. She was admitted for the last time, markedly dyspneic at rest, orthopneic, and with physical findings of pulmonary edema, peripheral edema and ascites. The pulse was rapid and blood pressure was unobtainable. Despite the intravenous infusion of levoarterenol and hydrocortisone, the patient expired ten hours after admission.

AUTOPSY FINDINGS

The autopsy was performed five hours after death. There was a grade 2 to 3 pitting edema of the lower extremities. The peritoneal cavity contained 5,000 ml. of clear ascitic fluid. Each pleural cavity contained approximately 400 ml. of clear transudate.

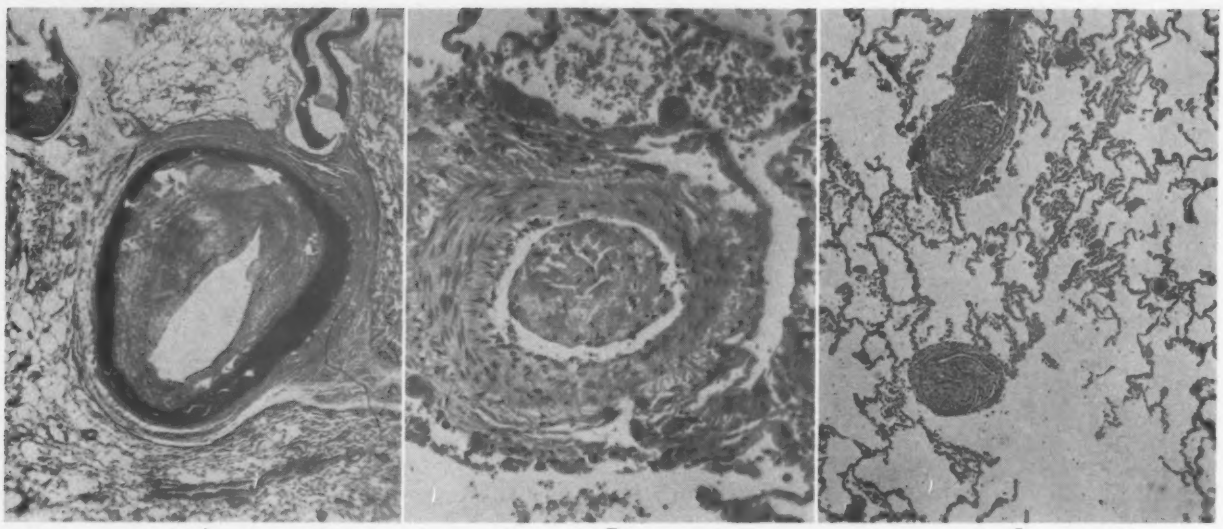
The heart weighed 400 gm. The right chambers were markedly enlarged. The right ventricle measured 1 cm. in thickness. The papillary muscles and columnae carneae of the right ventricle appeared stretched and thickened. The right auricular appendage contained a small mural thrombus. The tricuspid and pulmonic valve rings measured 13 cm. and 8 cm. in circumference, respectively. The valvular cusps were thin and delicate.

The main trunk of the pulmonary artery showed multiple subintimal yellowish plaques scattered throughout.

The right lung weighed 430 gm. and the left 400 gm. On cut section, the parenchyma was dark brownish red. A recent small infarct was found in the lower lobe of each lung. In connection with these infarcts, occlusion of a tertiary radicle of the pulmonary artery was found in each lung. The branches of the pulmonary artery showed a moderate degree of arteriosclerotic changes.

The pelvic venous plexus contained multiple small cylindrical thrombi.

Microscopic: The main histologic findings were present in the lungs (Fig. 4). The parenchyma showed a moderate degree of acute congestion and mild emphysema. Terminal branches of the pulmonary arteries contained thrombi in different stages of organization. The arteries and arterioles showed marked thickening of their walls due to circumferential and eccentric subintimal fibrosis. Only two of the medium caliber arterioles were occluded by recent emboli with hemorrhagic infarction of the



A B C

FIG. 4. A, small branch of the pulmonary artery showing thickening of the elastica and eccentric subintimal fibrosis (Verhoeff elastica, × 10). B, small branch of the pulmonary artery occluded by partially organized embolus (hematoxylin and eosin, × 100). C, two small arterioles occluded by organized emboli (hematoxylin and eosin, × 30).

parenchyma. Section from the pelvic venous plexus revealed recent and organized thrombi.

COMMENT

The problem of the existence of primary pulmonary hypertension is as yet not solved. The clinical picture characteristic of such an entity has been defined in several reviews.[5-8] Essentially, in a young adult it is characterized by sudden onset of exertional dyspnea, fatigue, syncope and chest pain. The chief findings are slight cyanosis, accentuated P_2 and progressive intractable right heart failure; isolated right ventricular hypertrophy on x-ray examination and the pattern of right ventricular strain or hypertrophy on electrocardiography. The right heart catheterization reveals a markedly elevated pulmonary artery pressure with normal capillary pressure, absence of shunts, absence of gradient across any of the valves, evidence of diminished cardiac output and increase of total pulmonary resistance.

The case we are presenting was diagnosed prior to catheterization as being one of rheumatic heart disease with mitral stenosis. The data obtained on right and left heart catheterization rendered such a diagnosis untenable. In the absence of any known cause of cor pulmonale, the diagnosis of primary pulmonary hypertension seemed the most logical.

Autopsy suggested (1) that pulmonary hypertension was secondary to multiple pulmonary thromboses; and (2) that these were the result of emboli detached from veins of the pelvis, where multiple thrombi were discovered. It is impossible to state whether or not the pelvic thromboses were a complication of the previous gynecologic intervention. However, this seems likely.

We believe that this case emphasizes the difficulty of diagnosing primary pulmonary hypertension during life. Our findings in this case indicate that, even in the absence of clinically manifest thromboembolic disease, patients with similar clinical manifestations should have the benefit of long term anticoagulant treatment. The risk of such treatment is minimal and its value in long-standing congestive failure has been established. While it would be of help in cases with thrombophlebitis and embolic phenomena, it certainly would not be detrimental in primary pulmonary hypertension in which intravascular thrombosis is a possible complication.

SUMMARY

1. A case clinically diagnosed as primary pulmonary hypertension and studied with left and right heart catheterization is presented.

2. Necropsy evidence of extensive pulmonary vascular disease and pelvic vein thrombosis led to a change in diagnosis to pulmonary hypertension secondary to thromboembolic obliterative vascular disease.

3. The diagnosis of primary pulmonary hypertension cannot be made by exclusion despite both left and right heart catheterization.

ACKNOWLEDGMENT

The authors wish to thank the Department of Pathology of Mount Sinai Hospital for the histologic study of this case

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Diagnostic Shelf

A-V Dissociation with Interference in Transient A-V Block and Left Bundle Branch Block*

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CASE HISTORY

THE patient, a sixty-eight year old housewife, was admitted to the hospital because of sudden onset of headache, dizziness and blurring of vision. For one year she had been complaining of nocturia and occasional dyspnea. At the age of fifteen years, she had had diphtheria complicated by myocarditis. Since then, she had noted a slow pulse. Arterial hypertension was revealed at the age of sixty years.

Physical examination revealed a sixty-eight year old white woman in good general condition. Temperature was 98°F.; blood pressure, 265/110 mm. Hg in both arms; pulse, 40 per minute and irregular; respirations 32 per minute. The eyegrounds showed grade I arteriosclerotic changes of the retinal vessels. The veins in the neck were not enlarged; the thyroid gland was not felt. The chest was normal. No cardiomegaly was present. A grade II soft, systolic murmur was present at the apex; A_2 was louder than P_2; the rhythm was irregular. The edge of the liver was felt two fingerbreadths below the right costal margin and was soft and nontender. No peripheral edema was present.

Results of routine laboratory tests were within normal limits. Chest x-ray film revealed moderate cardiomegaly with calcification in the arch of the aorta. The hilar shadows, lung fields and costophrenic angles were normal.

The patient was treated with bedrest, low salt diet and Rauwolfia preparations. Blood pressure stabilized at 200/100 mm. Hg and she improved subjectively.

ANALYSIS OF THE ELECTROCARDIOGRAM

The electrocardiogram revealed a complex arrhythmia and QRS complexes which were of two types, which are to be referred to as A and B (Fig. 1). *Complexes A* are independent of the P waves. $\hat{A}QRS = -15°$ with a duration of 0.12 second; AT = 35°; Q-T = 0.48 second. Cycles are regular at 41 per minute. *Complexes B* are preceded by P waves with P-R intervals varying from 0.24 to 0.32 second. $\hat{A}QRS = -25°$ with a duration of 0.14 second; $\hat{A}T = 155°$; Q-T = 0.51 second. Cycles are irregular with an average frequency of 43 per minute. The A complexes have a pattern consistent with left ventricular hypertrophy; B complexes have a pattern suggesting left bundle branch block.

Esophageal Lead: The relationship between the P waves and the two types of ventricular complexes is best revealed by the esophageal lead at the atrial level, recorded simultaneously with lead V_1 (Fig. 1). The rate of the atrial complexes due to sinus impulses is 79 per minute. The cycles vary between 0.71 and 0.88 second with an average duration of 0.76 second.

The relationship of atrial to ventricular complexes reveals *A-V dissociation with interference.* When capture occurs, the ventricular complex assumes the form of complete left bundle branch block (complexes B).

Effect of Exercise: After exercise (Fig. 2), ventricular captures are seen to occur more frequently and regularly. In addition, there is a transient appearance of an idioventricular rhythm (complexes C).

Effect of Digitoxin and Eyeball Pressure: Five minutes after the intramuscular injection of 0.5 mg. of digotoxin (Fig. 3), the P-P intervals become regular at 0.8 second with a rate of 50 per

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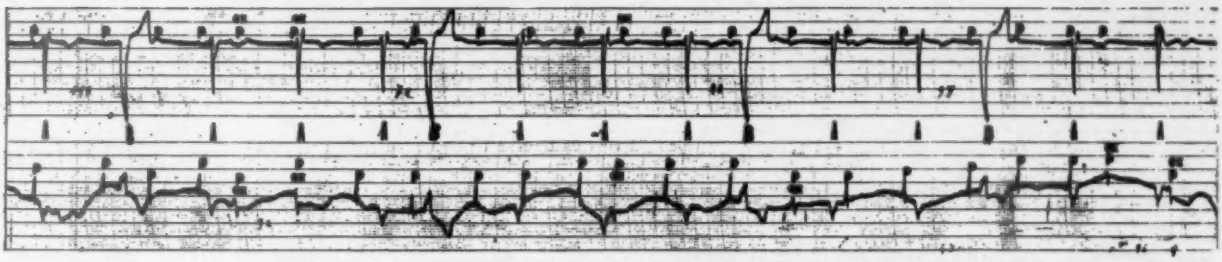

FIG. 1. Lead V_1 (above) and esophageal lead recorded simultaneously.

FIG. 2. Electrocardiogram after two-step exercise test, lead aVF (above) and esophageal lead (below) recorded simultaneously.

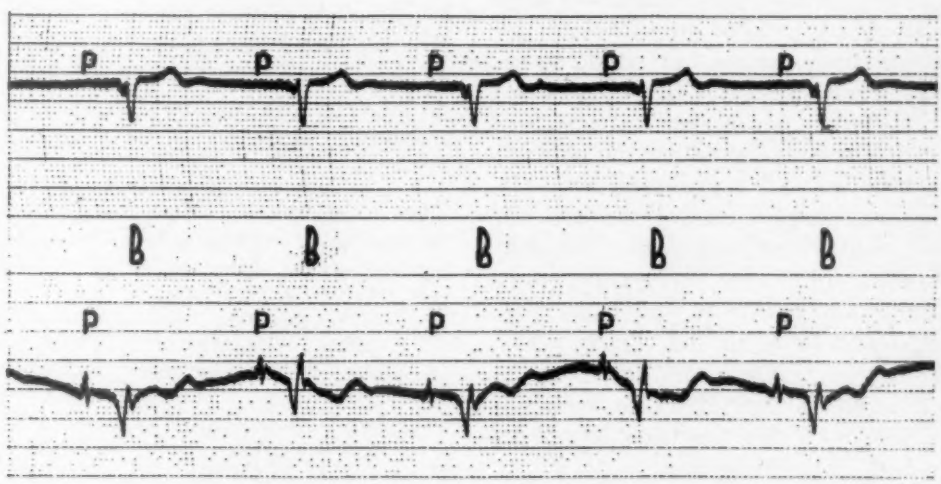

FIG. 3. Record five minutes after intramuscular administration of 0.5 mg. digitoxin. Lead aVF (above) and esophageal lead (below).

minute. The QRS complexes also become regular at 0.8 second with a rate of 50 per minute and the morphology is of the B type. The A-V dissociation disappears and a first degree A-V block is recorded (P-R = 0.21 second). Soon after compression of the eyeballs, complete A-V dissociation reappears (Fig. 4).

COMMENTS

It is difficult to decide whether the A-V dissociation had been present since the patient was fifteen years of age when she had diphtheria or whether it appeared subsequently. Even in the absence of previous electrocardiographic tracings, the history of the slow pulse since that age might favor the first assumption.

Cases of *unstable A-V block* have been previously described.[1-3] Of interest are the observations of the disappearance of a left bundle branch block when the A-V block becomes complete and the reappearance of the same bundle branch block when the conduction is normal. In our case, the esophageal lead showed that a left bundle branch block was present whenever the stimulus was conducted from the atria. On the other hand, when the atrial impulse was blocked (complete A-V dissociation) the pattern of bundle branch block disappeared. In view of the history, an organic lesion of the conducting bundle was assumed. In the absence of histologic demonstration, the conduction disturbance can be explained, according to Katz and Pick,[4] on

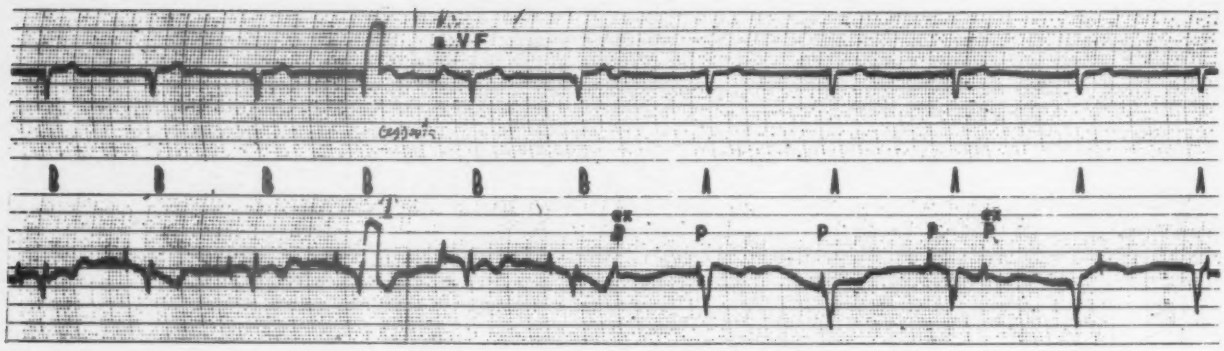

FIG. 4. Record immediately after eyeball compression. Lead aVF (above) and esophageal lead (below).

the basis of Mahaim's "paraspecific fibers." In this case, the atrial excitations would bridge the interruption of the bundle of His, traveling along the paraspecific fibers and would reach the right branch, then the electrocardiogram would show the pattern of left bundle branch block. On the other hand, when the A-V dissociation was total and the atrial impulses failed to stimulate the ventricles a subsidiary pacemaker would function. Then the impulses probably would arise in a supraventricular pacemaker because the ventricular rate was between 40 and 50 and the ventricular complexes were not aberrant.

The electrocardiographic tracings showed not only that the ventricular activations initiated above the A-V junction were proceeding along ordinary conduction pathways, but also that there was no left bundle branch block. The electrocardiographic pattern of left bundle branch block could be explained only by a delayed conduction in the interventricular septum according to Sodi-Pallares' studies.[5]

Recent investigations by Lev and Lerner[6] confirmed the existence of "paraspecific fibers," previously described by Mahaim and others, but the authors could not prove that these fibers were able to conduct the stimulus.

SUMMARY

In a case of A-V dissociation with interference and first degree A-V block, left bundle branch block was observed only in the beats conducted from the atria. This was attributed to "paraspecific fibers."

The A-V dissociation possibly was caused by diphtheritic myocarditis when the patient was fifteen years of age but myocardial changes due to hypertension and arteriosclerosis could not be excluded.

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Workmen's Compensation for the Cardiac

Can Moderately Heavy Work Cause an Attack of Acute Coronary Occlusion?*

LOUIS H. SIGLER, M.D., F.A.C.C.†
Brooklyn, New York

IN THIS paper I will discuss the seventh and last question of the Morland Commission submitted to cardiologists and internists with reference to causal relationship of strain and cardiac disability.[1] The question reads as follows: "*Assume that a man about twenty-five years of age begins employment at moderately heavy work and continues in this job for twenty years. At the end of this time, while on the job and without engaging in any unusual exertion or strain, he suffers a coronary occlusion with myocardial infarction. In your opinion, is the heart attack causally related to the employment?*"

Three hundred and eighty-one physicians answered this question. Of these, 353 or 92.7 per cent said no, twenty-eight or 7.3 per cent said either yes or that the work was an aggravating factor and one said it was possible. Of those who answered no, some based their answer on the assumption that there is no connection between occupation and the incidence of disease or the age at which the subject is stricken. Others believed that the incidence of coronary occlusion is lower in persons who engage in heavy work than in light work. Most physicians believed that the subject had pre-existing progressive coronary disease which reached a vulnerable stage and it was fortuitous that he happened to be at his employment when the disease process in the vessel became "ripe" and resulted in blockage.

STRESS, STRAIN AND ACUTE CORONARY ATTACKS

In a previous communication[2] I pointed out that work may be one of many underlying causes of coronary atherosclerosis. I stressed the fact that it is not the physical work alone but other factors in connection with work which may predispose to the disease. Of these may be mentioned anxieties, emotional stress, competitive drive, indoor confinement with insufficient ventilation, inhalation of vitiated air and other work factors. I also stated that there are a great many conditions other than work which are operative in the production of coronary atherosclerosis, most of which are still unknown. For these reasons a chronic pathologic process such as coronary atherosclerosis that may develop over a period of years cannot be definitely considered causally related to work although work cannot be eliminated as one of the causes.

When atherosclerosis of the coronary arteries reaches a vulnerable phase, an acute episode of coronary occlusion or of coronary insufficiency may develop under *any provocative cause*. I do not agree with the usual belief that these acute attacks are spontaneous in nature. I believe that nothing occurs spontaneously in biologic processes. That we are often not able to determine the underlying cause or causes of an acute episode of coronary disease is a lack of diagnostic

* The opinions expressed in this paper are those of the author and do not necessarily reflect the opinion of the American College of Cardiology or the Workmen's Compensation Committee.

† Chairman, Workmen's Compensation Committee, American College of Cardiology.

acumen on our part. Many of the attacks occur so soon after some event such as an exciting card game, a severe argument, watching a horse race or baseball game, running to catch a bus, mowing a lawn, shoveling snow and other events, that the provocative element can not be denied. Many of these factors do not involve litigation and causal relationship may thus be judged on unbiased opinion. There are also many intrinsic factors which may enter as provocative causes. Of these may be mentioned a heavy meal, postprandial lipemia, physical fatigue, insufficient rest, frightening dreams and others.

Of greatest importance is the individual reaction to strain. This depends upon the inherent constitutional and psychic state of the person, his general muscular and mental development in the course of his work, the state of health modified by infections, indiscretions in diet, tobacco intoxication, excessive use of alcoholic beverages, worrisome and depressing conditions in his home environment and other factors which may lower the resistance of the subject at a given time and predispose him to an attack.

To state that all the above factors have nothing to do with the onset of an acute occlusive process and that the attack at work is merely coincidental is to deny the fact that the human unlike the inanimate machine has feeling. I use the term "feeling" in a broad sense implying not only consciousness of internal bodily and external environmental conditions but also an unconscious sensitivity of all body tissues to internal and external nocuous stimulations. Every one of the billions of cells comprising the various body tissues is under direct and indirect influence of the nervous system modifying its activities either through contact or through chemical intermediation. A physical or mental strain occurring at a vulnerable period may thus directly or indirectly affect different structures or organs of the body, causing disturbances in the circulatory dynamics and local spasms of arterial segments particularly of the coronary system, which may result in acute structural changes.

Prolonged Work and Acute Coronary Occlusion

In the case under consideration, we must assume that prolonged, moderately heavy work over a twenty year period had some effect in the production of coronary atheromatosis although the percentage of contribution of work strain to such damage cannot be determined and therefore cannot be considered compensable. However, the acute attack which the patient had sustained while working certainly cannot be considered fortuitous. There were undoubtedly other elements on that day which were mentioned before, one of which may have contributed to the attack. The precipitating factor, however, was the work.

The assumption that there is no connection between occupation and the incidence or the age at which a subject is stricken is, I believe, unwarranted. This assumption is presumably based on statistical evidence which at best is fragmentary. The question as presented here does not take into consideration the given subject with his susceptibilities and his reactions to physical and emotional strain. The fact that relatively few persons have acute attacks after many years of strain such as was mentioned in the question, indicates that the individual reaction to the given strain as much as the strain itself is the factor to be considered.

The belief that the incidence of coronary occlusion is lower in people who engage in heavy work than in light work may be true. It undoubtedly applies to workmen who use nothing but physical power in their work. When we speak of work, however, we must consider not only physical work but also work requiring mental application and nervous tension, which play perhaps a greater part in the pathogenesis of the disease than mere physical labor. In this regard, the question posed in this paper cannot be logically answered. It stresses "moderately heavy work," not specifying the nature of the work—whether purely physical or combined physical and mental—and the extent of each factor. It does not tell us anything about the environment in which the work was done, the tension under which it was performed, the condition of the worker on that particular day and individual factors that must be considered. In other words, to logically answer the question posed in this paper we must take into consideration a great many unspecified factors which would individualize the given case.

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Progress Notes in Cardiology

Edited by EMANUEL GOLDBERGER, M.D., F.A.C.C.
New York, New York

Subaortic Stenosis

ALTHOUGH THE existence of a subaortic stenotic lesion of the left ventricular outflow tract was first described in 1832, its clinical diagnosis was of little more then academic interest until current surgical technics made the preoperative diagnosis and differentiation from aortic stenosis essential. Many believe it to be rare; however, current investigation suggests that it is much more commonly seen than hitherto supposed and that its diagnosis varies directly with clinical awareness of its existence and of the symptoms and signs resulting from the hemodynamic alterations it produces.

The pathogenesis of this abnormality is still subject to some controversy, but it would appear to be due to an arrest or atrophy of remnants of the primitive bulbus cordis, the major portion of which is incorporated into the infundibulum of the right ventricle. Thus, while embryonic arrest of growth of this primitive tissue on the right leads to infundibular stenosis of the right ventricular outflow tract, arrest of atrophy on the left results in subaortic stenosis of the left ventricular outflow tract.

An interesting study of subaortic stenosis has recently been made by Drs. Norman Brachfeld and Richard Gorlin (*Medicine*, 38: 415, 1959). In addition to the classically described congenital subaortic lesion, the existence of a hemodynamically more important muscular "systolic" or "functional" stenosis of the left ventricular outflow tract by congenital or acquired septal muscular hypertrophy is suggested by hemodynamic studies conducted by right and left heart catheterization at the time of surgery and through correlation with postmortem examination of six cases.

Classification: A classification of these two types follows:

I. Congenital [may or may not be associated with primary congenital myocardial hypertrophy of the septal portion of the outflow tract (remnant of bulbus cordis)
   - A. Band type (fibrous)
   - B. Diaphragmatic type (fibrous)

II. Acquired or developmental
   - A. Endocardial sclerosis secondary to trauma or mural inflammation
   - B. Muscular
     1. With subaortic stenosis
     2. With aortic stenosis, rheumatic or congenital
     3. With hypertension
     4. Miscellaneous
        - a. Bicuspid aortic valve
        - b. Coarctation of the aorta
        - c. Bacterial endocarditis
        - d. Idiopathic myocardial hypertrophy
        - e. Luetic aortitis

The importance of the antemortem diagnosis of subaortic stenosis is in the frequently fatal complications which attend this abnormality. Prior to the advent of antibiotic therapy the chief danger was bacterial endocarditis of the aortic valve or of the subaortic shelf. With reduction of these infectious lesions and a somewhat greater longevity, the type of complication has changed and evidences of persistent obstructive left ventricular cardiomegaly with resultant heart failure, angina pectoris, syncope and sudden death have become more frequent.

Differentiation: The differentiation of subaortic stenosis from aortic stenosis is still difficult. This lesion should be suspected whenever findings or x-ray examinations are atypical for classic aortic stenosis. Although no absolute single criterion exists for the diagnosis of subaortic stenosis, confirmation of a clinical suspicion can be obtained by a combination of the following factors:

I. History (early age of onset of murmur and thrill)

II. Physical examination
   A. Systolic murmur and thrill (atypical location, no systolic click)
   B. Aortic second sound (normal or loud)
   C. Diastolic murmur (present in 50 per cent of cases)
   D. Blood pressure (may be normal)

III. Electrocardiogram (little importance in differential diagnosis)

IV. X-ray findings
   A. Calcification of aortic valve (absent)
   B. First portion of the aorta (not dilated; no post-stenotic dilatation)

V. Arterial pulse tracing
   A. Anacrotism (rarely present)
   B. Percussion wave (early arrival, late peak systole)

VI. Left heart catheterization (three-chambered differential pressure gradient)

VII. Angiocardiography (radiographic identification of the subaortic stenosis)

Current surgical therapy of this lesion has proven inadequate and the mortality of operative cases misdiagnosed as aortic stenosis has been appreciable.

Book Reviews

The Surgeon and the Child, by Willis J. Potts. W. B. Saunders Co., Philadelphia, 1959, pp. 225, $7.50.

Dr. Potts states that *The Surgeon and the Child* is not a textbook of pediatric surgery. It is an easily read, well illustrated monograph which reflects the experience of the author and his staff in the rapidly expanding field of surgery in which the infant and the child hold the spotlight.

The author presents his philosophy of the practise of medicine in which "the religious beliefs, philosophies of life and economic conditions" of the parents must be considered. "It is difficult to measure devotion or to sound the depths of love for a living thing. Those who have been fortunate enough to have been spared the tragedy of a seriously deformed child are incapable of guiding or advising the unfortunate." The child-doctor relationship is discussed with humor and many good practical hints are presented to the uninitiated. The technical surgical aspects of specific anomalies and diseases are presented, ranging from the wide variety of gastrointestinal disturbances to tumors in children and including portal hypertension and atresia of the biliary duct. A good portion of the text is devoted to a discussion of those cardiovascular anomalies amenable to surgery, a field in which the author discourses from his position as an authority recognized throughout the world.

The introductory chapters, comprising some forty pages, are literary gems to be read and reread with delight. This reviewer believes that this section of the book should be compulsory reading for every medical student and all professional personnel who would accept any responsibility in the management of infants and children. The text, directed toward orienting obstetricians, pediatricians and general practitioners as well as pediatric surgeons, would benefit those parents whose children require hospitalization for surgical or nonsurgical ills.

SIDNEY BLUMENTHAL, M.D.

Les Hémiplégies Vasculaires, by Jean Minvielle and Boris Vlahovitch. Masson & Cie, Paris, 1959, pp. 228, 3800 fr.

An outline is presented of the problems raised by vascular hemiplegias: examination of the patient, etiology, physiopathology and therapy, including nursing and rehabilitation. This practical handbook is, therefore, addressed not only to the neurologist, neurosurgeon and cardiologist, but also to the internist and even more so to the general practitioner who is the first to see these conditions and upon whom rests the responsibility of referring those patients who can be improved by specific treatments to specialists.

Clearly and simply written, this handsomely presented book merits a place on the library shelves of everyone who reads French.

R. HEIM DE BALSAC

Hypertensive Disease: Diagnosis and Treatment, by Sibley W. Hoobler. Paul Hoeber Inc., New York, 1959, pp. 353, $7.50.

In the practice of medicine one of the more challenging situations is the diagnosis and treatment of hypertensive disease. Dr. Hoobler assembles in this book available data and knowledge on this subject, buttressed by his wide experience at the University of Michigan Hypertension Clinic. His presentation is most welcome to the practicing physician who will find practical guidance for treating his hypertensive patient. Case histories furnish examples of similar situations that the practitioner will encounter. The systematic approach to the multifaceted problems presented by hypertensive disease—the reduction of blood pressure, its maintenance at near normal levels, and the assessment of vascular vulnerability—are dealt with clarity and emphasis. The book is well written and adequately documented. Of particular interest is the excellent printing with bigger types than are ordinarily found, a point which the busy practitioner readily appreciates when referring to this book.

The treatment of hypertensive disease cannot yet be specific or simple but may be carried out in a hospital, in the clinic or at home. Curable types of secondary hypertension must be recognized and treated promptly. Cases of essential hypertension must be treated with the proper mental attitude and the appropriate hypotensive agent that controls the blood pressure without annoying or intolerable side effects. This complex phase of the management of hypertensive disease is clearly presented, and discussed by Dr. Hoobler, including the pharmacodynamics of the available drugs. At the end of the book, there are twelve appendices of precise technics for tests and outlines of treatment for the various hypertensive emergencies.

Naturally this book, like any other book on the subject, cannot possibly offer the last word on the little-understood problem of hypertensive disease. Indeed, the many controversial aspects in the problem including different experiences in the use of the various hypotensive drugs are pointed out clearly. It is understandable that Dr. Hoobler's recommendations in treatment are chiefly weighted toward his own experience. For this reason, the reader may have to read and consider the experiences of others until a final and standard form of treatment is agreed upon. Fortunately, Dr. Hoobler has wisely included in the appendices the plans of treatment by other workers. This makes the volume a more comprehensive treatise and offers the practicing physician a ready opportunity to know the experience of others.

The reviewer recommends this book to all physicians as a truly valuable reference in the complex problem of diagnosis and treatment of hypertensive disease.

MARIANO M. ALIMURUNG, M.D.

Autogenous Vein Grafts, by W. Andrew Dale. Charles C Thomas, Springfield, Ill., 1959, pp. 123, $6.00.

This is a well written, well arranged, completely documented analysis of the position of the autogenous vein graft in current arterial surgery. The basic hemodynamic concepts underlying the surgery of graft replacement are considered in relation to the subject of the monograph. The particular value of the vein graft is its autogenous origin. Neither the local tissue reaction nor the more complex allergic response to homografts complicate the autogenous replacement. Although objection can be made to some of the statements based on the publications of others, good judgment has been used throughout the presentation. For the surgeon interested in a succinct objective evaluation of the subject, this book is highly recommended.

LESTER BLUM, M.D.

Involution of the Ductus Arteriosus. A Morphological and Experimental Study, with a Critical Review of the Literature, by A. Sciacca and M. Condarelli. S. Karger Basel, New York, 1960, pp. 52, sFr. 7.

The authors of this monograph have undertaken a morphologic and functional study of the ductus arteriosus in the fetal guinea pig. This is preceded, in the first part, by an analysis of the prevailing views about the structural and functional basis for closure of the ductus arteriosus. Controversial theories are highlighted and the gaps in our knowledge of the exact mechanism of closure of the duct are stressed. Considerable space is devoted to a critical analysis of the experiments of Barcroft and of Ardran in sheep fetuses. The authors then set out to test the still prevalent view that the duct begins to close after birth by morphologic and experimental studies of guinea pig fetuses at varying gestational ages and in newborn guinea pigs. Morphologic investigations include measurements of the relative sizes of the duct and the pulmonary artery in fetuses of varying ages. Microscopic studies performed in serial sections supplement these measurements. The authors noted that in the last third of gestation a progressive diminution in the size of the duct relative to that of the pulmonary artery takes place. The first signs of involution of the duct were found long before birth, beginning with the appearance in the intima of an amorphous substance rich in mucopolysaccharides. At birth the lumen was often nearly or completely obliterated by young connective tissue. The effect of ligation of the ductus arteriosus on the right ventricle in fetuses twenty to thirty days before term or at term was compared with that of ligation of the main pulmonary artery. In previable fetuses ligation of the duct produced dilatation of the right side of the heart, while in fetuses at term it did not have this effect. Tying the pulmonary artery precipitated acute right cardiac dilatation regardless of fetal age. These observations

bear out the diminishing functional role of the duct during the latter part of intrauterine life in the guinea pig.

Angiocardiographic studies in guinea pig fetuses appeared to substantiate the authors' impressions gained from morphologic observations. Contrary to prevailing concepts they indicate that pulmonary circulation is fully established in the fetus at term. Although the authors express reservations about the ability to interpret angiocardiographic pictures, relatively much space is given to their reproduction. On the other hand, morphologic observations might have been illustrated in greater detail. Photomicrographs are of good quality; however, magnification and staining technic employed are not indicated in the legends. It might have been instructive to correlate the changing structure of the duct with that of the main pulmonary artery and with the development of the pulmonary vasculature at varying stages of fetal life. The monograph is well organized and clearly written. The plan of experimentation is well designed for correlation with observations on structure. A bibliography containing many contributions from the European literature is appended.

It will be interesting to compare this experimental study of the ductus arteriosus with observations in the human fetus and newborn. On the basis of observations in human autopsy material the reviewer would agree with the authors' point of view that morphologic closure of the duct is not a sudden event at the onset of pulmonary respiration, but that it begins in intrauterine life. Complete anatomic closure of the duct at birth, however, seems to be the exception in the human whose duct tends to retain a lumen for several weeks of postnatal life. Caution is necessary in drawing conclusions about functional closure of the duct based on anatomic observations alone. Angiocardiographic studies may provide the answer. The authors stress that the process of closure of the duct is quite independent of functional changes which might affect it at birth. This view finds support in observations of some congenital cardiac anomalies in infants, in whom persistent patency of the ductus arteriosus would be essential for continuation of life beyond the first few weeks. Nevertheless, the duct goes on to close at the expected time, quite unconcerned with hemodynamic forces which should tend to keep it open.

This study represents a valuable contribution to our knowledge of the normal involution of the ductus arteriosus. It is recommended particularly to those concerned with the physiology and changing pattern of the fetal circulation. From an understanding of the normal process of involution of the duct may come the answer to the question why in some individuals this process fails to take place in some persons. LOTTE STRAUSS, M.D.

RECEIVED FOR REVIEW

All books received will be acknowledged in this column. In so far as possible as space permits, books of special interest will receive more extensive reviews.

Clinical Vectorcardiography and Electrocardiograhy, by Edward Massie and Thomas J. Walsh. Year Book Publishers, Inc., Chicago, 1960, pp. 592, $27.50.

Toward the Diagnosis of Congenital Heart Disease, by Carleton Whiteside. Charles C Thomas, Springfield, Ill. 1960, pp. 86, $4.50.

Hypothermia for the Neurosurgical Patient, by Antonio Boba. Charles C Thomas, Springfield, Ill. 1960, pp. 124, $6.00.

A System of Medical Hypnosis, by Ainslie Meares. W. B. Saunders Company, Philadelphia, 1960, pp. 484, $10.00.

Nature of Rheumatic Heart Disease with Special Reference to Myocardial Disease and Heart Failure, by George E. Murphy. Williams & Wilkins Company, pp. 384, $3.50.

Struktur und Stoffwechsel des Herzmuskels. I. Symposion an der Medizinischen Universitäts-Klinik Munster (Westf.), by W. H. Hauss and H. Losse. Georg Thieme Verlag, Stuttgart, 1959, pp. 170, DM 29 ($6.90).

Cardiac Disease in Pregnancy, by Curtis Lester Mendelson. F. A. Davis Company, Philadelphia, 1960, pp. 385.

Clinical Applications of Cardiopulmonary Physiology, by Henry Williams, Jr. Paul B. Hoeber, New York, 1960, pp. 233, $7.50.

Heart Care. An Authoritative Guide by Twenty Experts edited by Morris Fishbein. Hanover House, New York, 1960, pp. 246, $2.95.

Clinics in Electrocardiography, by Dale Groom. Charles C Thomas, Springfield, Ill. 1960, pp. 152, $8.00.

Congenital Malformations of the Heart. Revised edition, Vol. I. General Considerations, by Helen B. Taussig. Harvard University Press, Cambridge, 1960, pp. 204, $4.75.

Surgery of the Aorta and Its Branches, by James P. Hardy. J. B. Lippincott Company, Philadelphia, 1960, pp. 386, $6.50.

Disease and the Advancement of Basic Science, edited by Henry K. Beecher. Harvard University Press, Cambridge, 1960, pp. 416, $12.50.

College News

President's Column

On January 12, 1961, your President, Past-president and Editor of the Journal, Dr. Simon Dack, attended the College Workshop which took place at the Peter Bent Brigham Hospital in Boston on January 11 through January 13. We were very sorry that our Executive Director, Dr. Philip Reichert, could not accompany us as he had planned.

Although Dr. Dack and I were able to spend only one day, we were tremendously impressed with the careful organization that had gone into the preparation of this Workshop and the friendly hospitality. Present at the Workshop were sixty-six members of the College representing fourteen states. We noted that several had come from as far as the Midwest and Florida.

As you know, this Workshop was organized under the direction of Dr. Dwight E. Harken, and I would like to quote a few paragraphs from Dr. Harken's letter of welcome to those attending:

"Dear Friends:

A hearty welcome to you! Please excuse this secretarial short cut to an individual note of greeting. We are delighted that you have come and flattered at the turnout. The plan was to accept a maximum of thirty. You are the largest group of thirty the world has ever known, but with inflation it is not so remarkable. You are a distinguished group and there should be some pleasure in getting acquainted with each other."

He closed the letter with these words . . .

"Thanks for coming. It is a joy to welcome you. I do hope you enjoy the meeting and profit from it.

Sincerely yours,
Dwight E. Harken, M.D."

We were told that the night before our arrival, Dr. Harken had entertained the visiting doctors and their wives at a cocktail party at his home.

You all had a chance to see the excellent program when it was announced. I might say that one of the features of this Workshop which impressed us was the strict adherence to a time schedule. No speaker went over as much as one minute of his allotted time and as a result there was plenty of opportunity for questions and discussion. In addition every session that we attended started promptly at the time scheduled and there were no delays at all. I have attended many medical meetings at which this was not adhered to and it was quite evident how important this was and how successfully it was carried out at the Boston Workshop.

It was a milestone in the history of the College to hold a Workshop in one of Boston's most famous hospitals, the Peter Bent Brigham. As we entered the hospital, we were very pleased to see a wonderful portrait of our distinguished Honorary Fellow, Dr. Samuel Levine. The College is indebted to Dr. Lloyd Mussells, Director of the Hospital, for extending its facilities to us. We realize how difficult it is for a hospital to feed sixty-five visiting doctors; and with the help of the gracious ladies of the Hospital Auxiliary, we enjoyed a most delicious luncheon.

That evening, following the scientific program, Dr. John Hartigan, who had worked out many details surrounding this large Workshop, arranged a most delightful informal dinner, preceded by a cocktail party, at the Statler-Hilton. The highlight of this dinner was the introduction by Dr. Samuel Levine of the Faculty of the Workshop in a most charming manner. Your President then had the opportunity to greet those present and report some of the year's activities of the College and, in particular, to bring them up-to-date on some of the plans for the New York Annual Meeting.

Louis F. Bishop, M.D.
President

Dr. Dwight E. Harken addressing the Boston Workshop group.

1961 Workshop Program

THERE are four remaining workshops open to registration.

Members of the College are urged to take advantage of this opportunity offered by your Postgraduate Education Committee by communicating with Dr. Philip Reichert, Executive Secretary, 350 Fifth Ave., New York 1, New York, relative to arrangements for participation. Due to the limited number of participants for each workshop, early registration is advised.

February 23, 24, 25	Dr. E. Sterling Nichol and associates	Acute and life-long anticoagulant therapy routines; care of acute and chronic nonsurgical cardiac problems	Miami Heart Institute, Miami Beach, Fla.	3
March 6	Dr. Louis F. Bishop	Office cardiology	141 East 55th St., New York 22, N. Y.	2
March 30, 31	Dr. Samuel Bellet and associates	Fibrinolysin, cardiac arrhythmias and cardiac catheterization	Heart Station, Philadelphia General Hospital, Philadelphia, Pa.	4
May 2	Dr. Don L. Fisher and associates	Left and right heart catheterization	Cardiopulmonary Laboratory, Allegheny General Hospital, Pittsburgh, Pa.	2

Announcements

Cardiology Course

A course in Cardiology (Rheumatic Fever, Rheumatic Heart Disease and Congenital Heart Disease) for general physicians and specialists, sponsored by the Michigan Heart Association and The University of Michigan Medical Center, will be given March 13 to 17, 1961, at the University Hospital, Ann Arbor, Michigan.

In addition to a number of eminent speakers from the State of Michigan, the following guest lecturers will participate: Richard J. Bing, M.D., Detroit; S. Gilbert Blount, M.D., Denver; Eugene W. Braunwald, M.D., Bethesda; Jesse E. Edwards, M.D., St. Paul; Earl B. Kay, M.D., Cleveland; John Kirklin, M.D., Rochester, Minn.; George Murphy, M.D., New York; Charles H. Rammelkamp, M.D., Cleveland; Will Sealy, M.D., Durham; Gene H. Stollerman, M.D., Chicago; May G. Wilson, M.D., New York.

For further details, write to Dr. John M. Sheldon, Director, Department of Postgraduate Medicine, University Hospital, Ann Arbor, Michigan.

Sub-Board of Pediatric Cardiology

The Sub-Board of Pediatric Cardiology of the American Board of Pediatrics announces that its organization is complete and that it is now ready to accept applications for certification both on record and by examination. The former must be submitted by December 31, 1961.

Applications for approval of residency-training programs in pediatric cardiology will also be accepted.

Full information and application forms may be obtained from: The Executive Secretary, American Board of Pediatrics, 6 Cushman Road, Rosemont, Pennsylvania.

The members of the Sub-Board of Pediatric Cardiology are: James W. DuShane, M.D., Chairman, Rochester, Minn.; Forrest H. Adams, M.D., Los Angeles, Calif.; Edward C. Lambert, M.D., Buffalo, N. Y.; Alexander S. Nadas, M.D., Boston, Mass.; Saul J. Robinson, M.D., San Francisco, Calif.; and Helen B. Taussig, M.D., Baltimore, Md.

YOUNG INVESTIGATORS' AWARD

The American College of Cardiology is pleased to announce the establishment of an award for excellence to be entitled:

"THE YOUNG INVESTIGATORS' AWARD OF THE AMERICAN COLLEGE OF CARDIOLOGY"

THIS AWARD IS REPRESENTED BY A SILVER MEDAL AND $1,000.

The conditions of the award are:

ELIGIBILITY — Any physician in residency or fellowship status or within 3 years following his residency or fellowship.

SCOPE — A formal presentation, 10 minutes in length, describing original investigation in which the contestant did either the work or was a significant member of investigating team.

PROCEDURE — An original manuscript and letter indicating intention to enter the competition must be in hands of Executive Director by *March 1, 1961.*

An *accompanying* letter from the chief of the service or laboratory indicating his willingness to have the material presented in the competition.

Judging to be made by the Committee of Judges selected by the President of the American College of Cardiology and their decision to be based upon (a) excellence and orginality of investigation (b) excellence of written manuscript (c) excellence of presentation.

Competition to be in New York City upon the occasion of the 10th Annual Meeting of the American College of Cardiology, date May 17 to 20, 1961.

Address queries and manuscript to: Executive Director, American College of Cardiology, Empire State Building, 350 Fifth Avenue, New York 1, New York.

PUBLISHER'S INFORMATION PAGE

The Editors and Publishers of THE AMERICAN JOURNAL OF CARDIOLOGY welcome concise articles on new findings in cardiology. As is customary in professional publications, statements in articles are the responsibility of the authors; articles must be contributed solely to THE AMERICAN JOURNAL OF CARDIOLOGY; material is copyrighted and may not be reproduced without permission of the publishers.

Preparation of Manuscripts

Authors are requested to follow these instructions carefully in preparing manuscripts: Please double space with good margins; type on one side of the sheet only; make a carbon copy for yourself and send the original with one carbon copy to the editor; include staff position and connection; list bibliographic references in chronological order as referred to in text at the end of the article (not in footnotes). Please make certain each reference contains the name of author with initials; title of article; name of periodical, with volume, page and year. For example: Smith, J. S. Treatment of cardiac failure. Am. J. Card., 3:274, 1959.

Preparation of Illustrations

So that your article will be presented most effectively, illustrations must be glossy prints or professional drawings in black ink (never in blue; it will not reproduce well). Reference to all illustrations should be inserted in the text in consecutive order. Please follow these identification instructions: Write the figure number and the author's name on the back of each illustration and indicate the top.

Type legends for illustrations on a separate sheet with numbers corresponding to those on the photographs or drawings. Please do not attach legends to the pictures.

A reasonable number of illustrations are supplied free of cost; we know the authors will understand that special arrangements must be made with the publishers for excess illustrations and tables.

Reviews, Abstracts

Books for review may be sent directly to the Editor, Simon Dack, M.D., **The American Journal of Cardiology,** 11 E. 36th St., New York 16.

Permission to abstract must be obtained from the publisher. Only paid circulation journals will be permitted to abstract.

Reprints

Orders for reprints of articles should be sent directly to the Publisher, **The American Journal of Cardiology,** 11 East 36th Street, New York 16, N. Y. After February 25, 1961, our address will be 466 Lexington Ave., New York 17, N. Y. Prices are quoted after articles are published.

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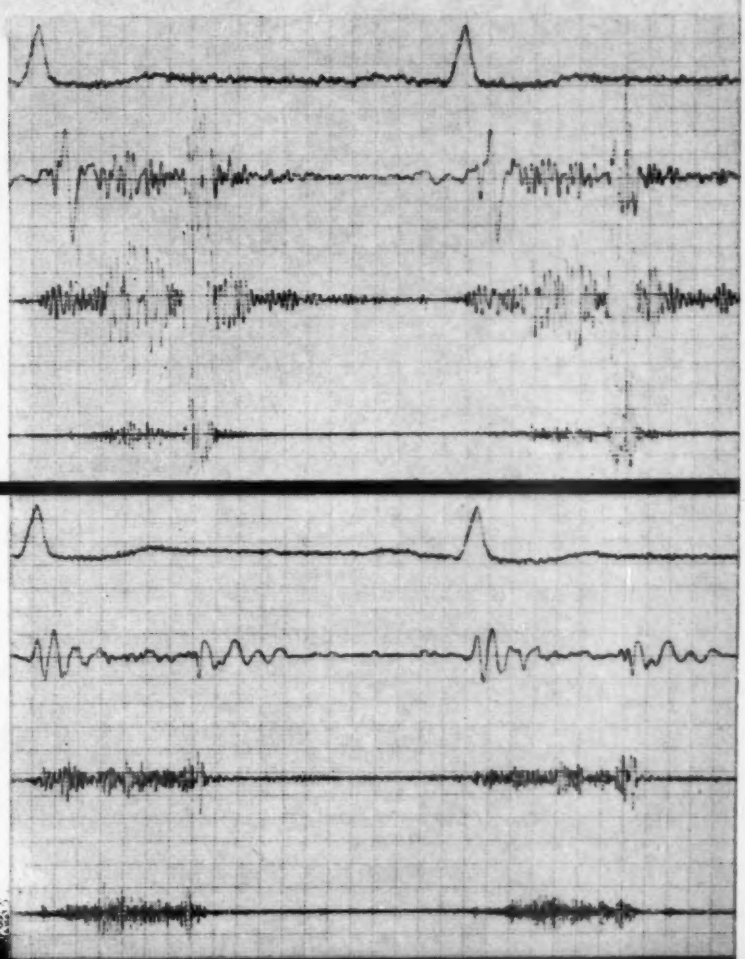

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*U. S. Patent 2,895,881

1. Greif, E and Scheuer, J.: J Mount Sinai Hosp., Nov./Dec. 1960

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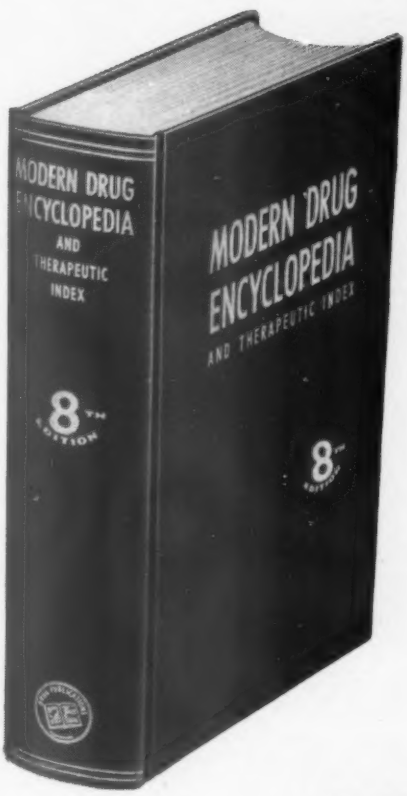
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BIBLIOGRAPHY 1. Ford, R. V., Clinical-Pharmacologic Investigation of Methyclothiazide, a New Oral Diuretic; Comparative Clinical Effects of Hydrochlorothiazide and Methyclothiazide, Current Therap. Res., 2:422-430, Sept., 1960. 2. Bryant, J. M., Schwartz, N., Fletcher, L., Jr., Fertig, H., Schwartz, M. S., McDermott, J. D., Quan, R., Clinical Studies of the Anti-hypertensive Effects of a New Benzothiadiazine Diuretic, submitted for publication.

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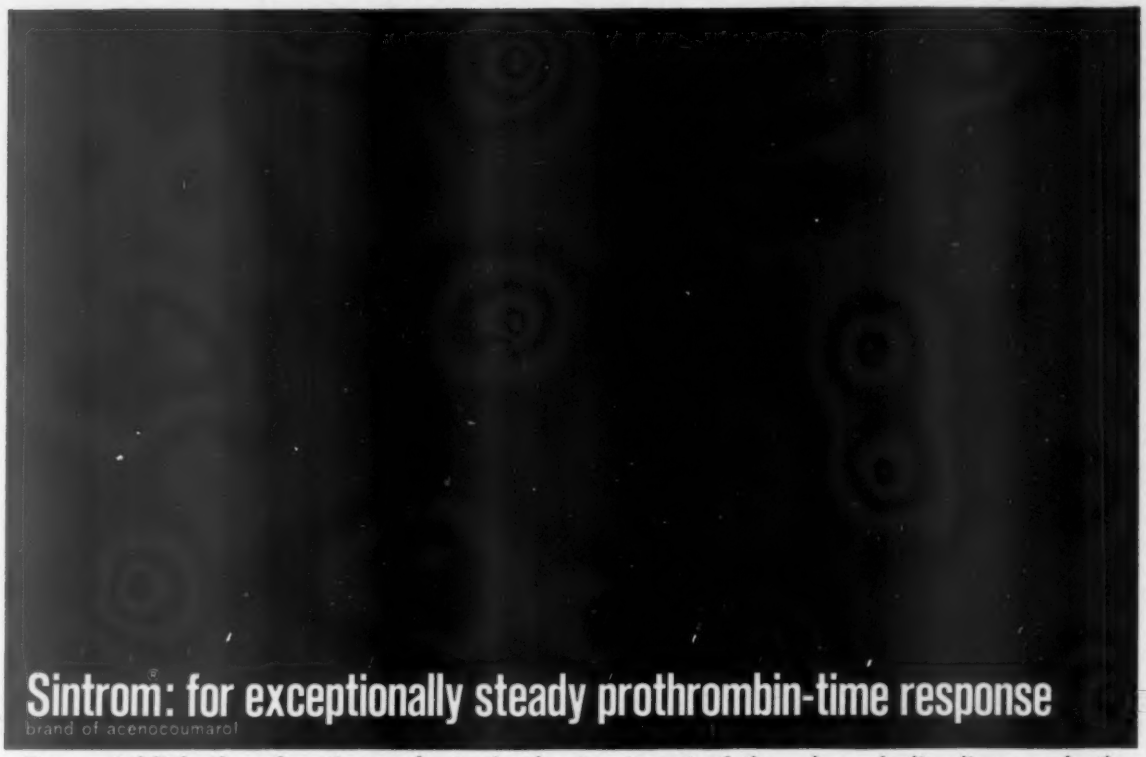

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(Russek, H. I., Am. J. Med. Sc. Feb., 1960)

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CLINICAL OPINION

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1. Riseman, J.E.F., *et al.*: Circulation *17*:22 (Jan.) 1958.

2. Russek, H.I.: Circulation *18*:774 (Oct.) 1958.

3. Hirshleifer, I., *et al.*: Scientific Exhibit, A.M.A., Atlantic City, N. J., June, 1959.

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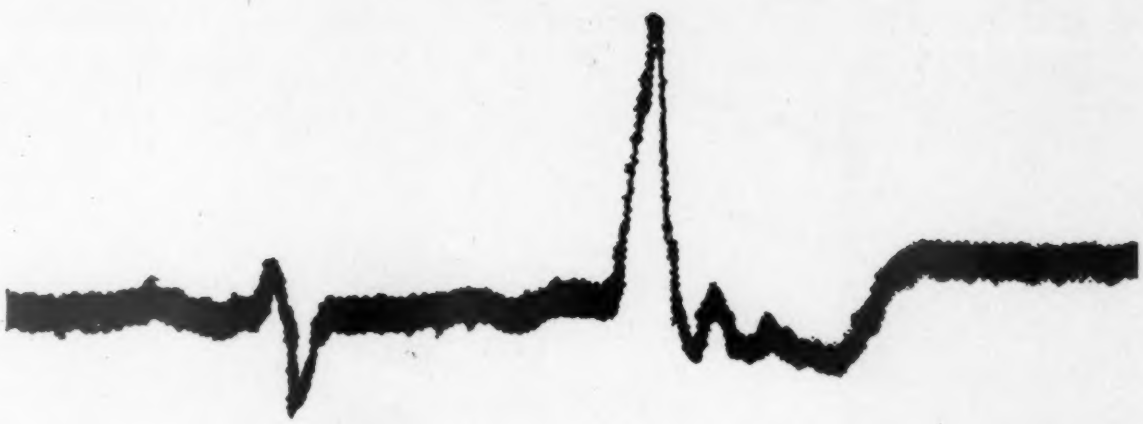

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References: 1. Zapata-Diaz, J., et al.: Am. Heart J. 43:854, 1952. 2. Modell, W.: In Drugs of Choice, C.V. Mosby Co., St. Louis, 1958, p. 454.
3. Kayden, H. J., et al.: Mod. Concepts Cardiovasc. Dis. 20:100. 1951. 4. Miller, H., et al.: J.A.M.A. 146:1004, 1951.

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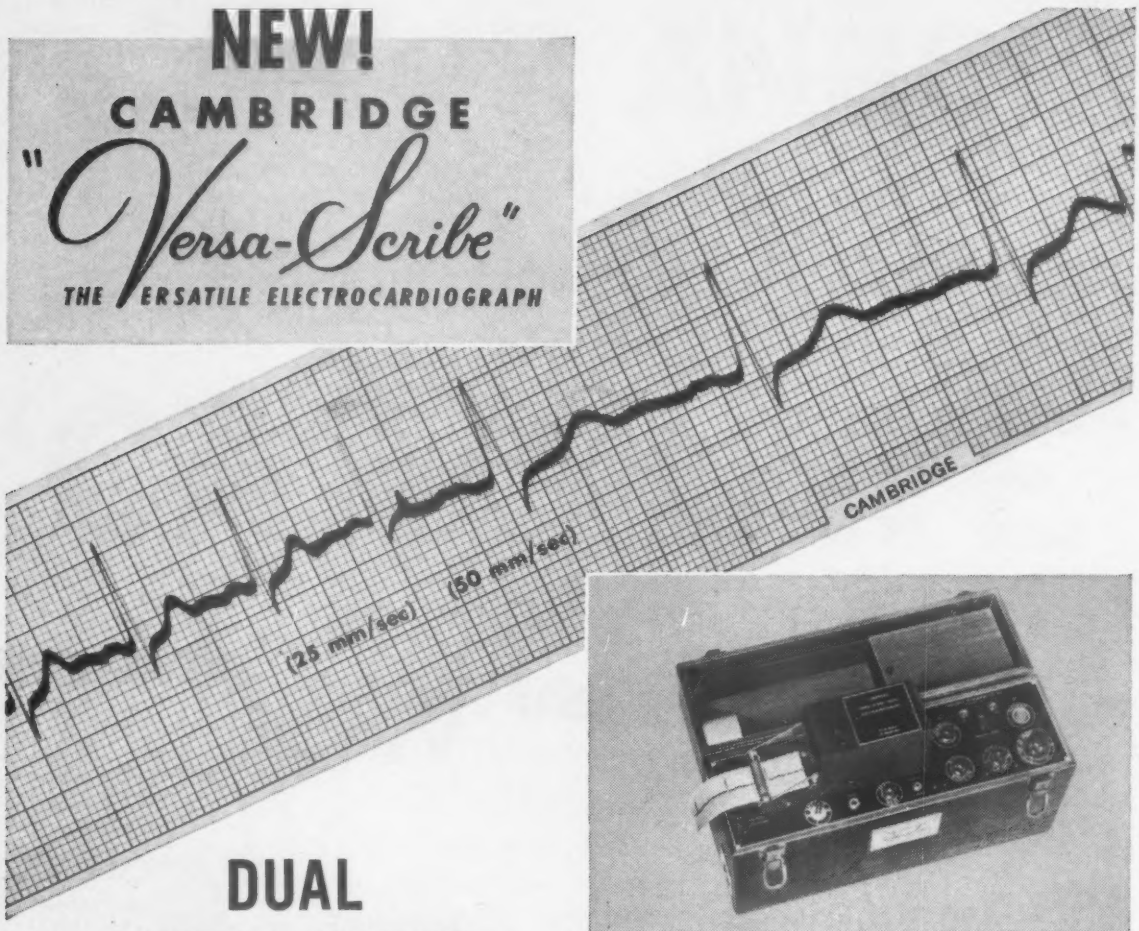

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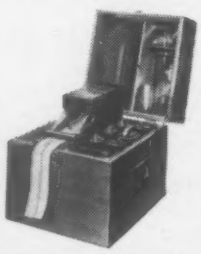

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1. Boer, S., et al.: J.A.M.A. 167:704, June 7, 1958.
2. Moser, K. M.: Disease-a-Month, Chicago, Yr. Bk. Pub., Mar., 1960, p. 13.

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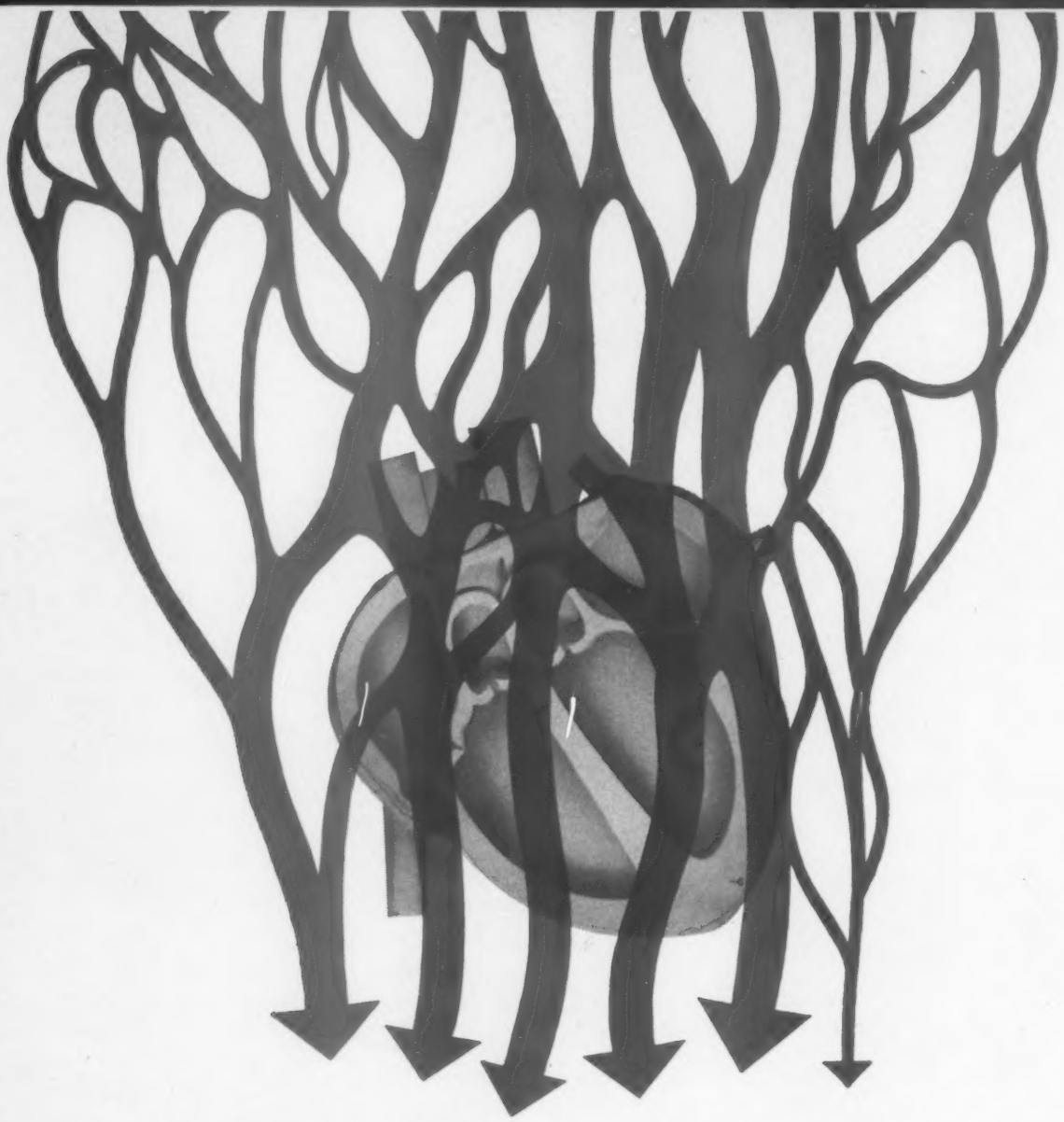

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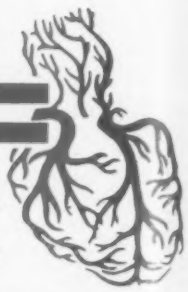

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Leslie, R.E.: Coronary Vasodilators—A Comparative Study (to be published)

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Fisch, S.; Boyle, A.; Sperber, R.; De Graff, A.C.: A Critical Review of Methods Used In Evaluating So-Called Coronary Vasodilators in Man, paper presented at the American Therapeutic Society Annual Meeting, Miami Beach, Florida, June 10, 1960.

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Albert, A.: Chronic Coronary Insufficiency—Its Treatment with a New Drug (to be published)

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Advertisers' Product Index

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Abbott Laboratories
Enduron*.....*Insert facing page* 40

Amfre-Grant Inc.
Corovas*..... 46

Armour Pharmaceutical Company
Pentritol Tempules*..... 29

Best Foods, Div. Corn Products Company
Mazola Margarine..... 25

The Burdick Corporation
Cardiac Equipment..... 44

Burroughs Wellcome & Co., Inc.
Cardilate*..... 48
Lanoxin*..... 30

Cambridge Instrument Co.
Cardiac Equipment..... 50

Ciba Pharmaceutical Products, Inc.
Serpasil-Apresoline*..... 58

Doubleday & Company, Inc.
Medical Book..... 31

Electrodyne Co., Inc.
Cardiac Equipment..... 15

Endo Laboratories
Coumadin*..... 51

Geigy Company
Hygroton*..... 19
Sintrom*/Tromexan*..... 43

Ives-Cameron Company
Isordil*..... 54

Thos. Leeming & Co., Inc.
Clarin*.....Third Cover

Eli Lilly & Company
Crystodigin*..... 34

Merck Sharp & Dohme, Div. Merck & Co., Inc.
Aqua-Mephyton*.....22–23
Aramine*.....52–53
Hydropres*.....26–27

The Wm. S. Merrell Company
Mer/29*.....32–33

Ortho Pharmaceutical Corp.
Actase*.....Inside Front Cover

Pitman-Moore, Div. of Allied Laboratories
Emdee Margarine.....*Insert facing page* 16

Riker Laboratories, Inc.
Lipo-Hepin*.....Fourth Cover

Roche Laboratories, Div. of Hoffman-La Roche Inc.,
Marplan*..... 8

J. B. Roerig & Co., Div. Chas. Pfizer & Co., Inc.
Cartrax*..... 12

Sanborn Company
Viso-scope..... 20

Schering Corporation
Miradon*..... 57

Schick X-Ray Company, Inc.
Cardiac Equipment..... 37

G. D. Searle & Co.
Aldactone*..... 1

Sherman Laboratories
Elixophyllin*..... 45

E. R. Squibb & Sons, Div. of Mathieson Chemical Corp.
Naturetin*/Naturetin c̄ K*..... 14
Pronestyl*..... 49

Charles C Thomas, Publisher
Medical Books..... 16

United States Catheter & Instrument Corp.
Cardiac Catheters & Instruments..... 40

Walker Laboratories Inc.
Hedulin*..... 2

Wallace Laboratories
Deprol*..... 47
Miltown*..... 6
Miltrate*..... 21
Miluretic*..... 24

(Continued on next page)

*** Complete description of starred drugs will be found in MODERN DRUGS and THE MODERN DRUG ENCYCLOPEDIA**

Warner-Chilcott Laboratories
Peritrate*..... 4

White Laboratories, Inc.
Gitaligin*..... 28

Winthrop Laboratories
Alvodine*..... 10

Wynn Pharmacal Corp.
Aminophylline..... 13
Quinaglute*..... 38

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References: (1) Blaustein, A.: New York J. Med. *58*:701, 1958. (2) Lange, K., *et al.*: Am. Heart J. *55*:73, 1958. (3) Kellaway, G.: Brit. M. J. *2*:889, 1958. (4) Connell, W. E. and Mayer, G. A.: Canad. M.A.J. *80*:785, 1959. (5) Paul, H. A., Arscott, P. M., Koppel, J. L., and Olwin, J. H.: Surg. Gynec. & Obst. *108*:605, 1959.

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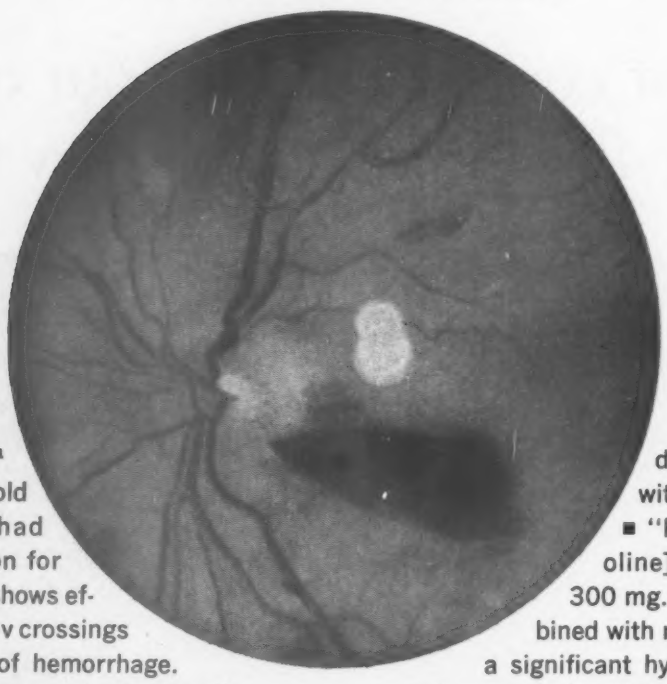
When blood pressure must come down



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1. Bedell, A. J.: Clin. Symposia 9:135 (Sept.-Oct.) 1957.
2. Lee, R. E., Seligman, A. M., Goebel, D., Fulton, L. A., and Clark, M. A.: Ann. Int. Med. 44:456 (March) 1956.

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1. California Med. *91*:327 (Dec.) 1959.
2. Clin. Res. 7:388, 1959.

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